

Short-Term Treatment Effects of a Substance Use Disorder Therapy Involving Traditional Amazonian Medicine

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ABSTRACT

Chronic illness management today commonly involves alternative medicines. Substance use disorder (SUD), as a chronic psychosomatic illness, might benefit from a similar approach. The accredited Takiwasi Center offers such an SUD treatment program involving Amazonian medicine combined with psychotherapy. The current study assessed this integrative program's short-term therapeutic effects. We measured baseline data from 53 dependence-diagnosed males admitted to treatment (T1) and repeated clinical outcome variables at treatment completion (T2). Paired samples t-tests were used to assess changes between T1 and T2 ($n = 36$). Nearly all participants (age $M = 30.86$, $SD = 8.17$) were dependent on multiple substances, most prominently cannabis, alcohol, and cocaine-related drugs. A significant decrease (T1 to T2) was found for addiction severity outcomes drug use ($p < .001$), alcohol use ($p < .001$), psychiatric status ($p < .001$), and social/familial relationships ($p < .001$). Emotional distress also diminished significantly ($p < .001$), as did substance craving ($p < .001$). Quality of life increased significantly from T1 to T2 ($p < .001$). Our results provide first indications for significantly improved SUD symptoms after the Amazonian medicine-based treatment. These findings are preliminary given the design, but strongly encourage further investigation of this therapy, which in the long term may open new therapeutic avenues for SUDs.

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Background

Substance use disorder (SUD) is a large-scale public health problem that continues to affect global modern society. It is associated with extensive costs and adverse consequences, including health impairments, accidents, and early death (Gowing et al. 2015). Today SUD is increasingly understood as a chronic illness, due to the disorder's persistent nature, characteristic tendency for relapse, and on the basis of neurobiological evidence showing long-term cerebral adaptations associated with regular drug use (Brandon, Vidrine, and Litvin 2007; Koob and Le Moal 2008). Nonetheless, existing treatments for SUD are frequently delivered as if for an acute condition (McLellan et al. 2000; White, Boyle, and Loveland 2002). It has been suggested, therefore, that SUD therapy could benefit from more alignment with state-of-the-art health-care models that are being employed in somatic medicine for chronic illnesses (McLellan et al. 2000). Present day chronic illness management is often integrative and may, for example, involve referral protocols for patients to access therapies other than biomedical, such as acupuncture,

osteopathy, or homeopathy (for instance in the case of chronic musculoskeletal pain; Jong et al. 2016). Thus, chronic care today increasingly combines conventional treatments with alternative or traditional medicines (Molassiotis et al. 2005; Templeman and Robinson 2011; World Health Organization 2013), a model that could be beneficial also for SUD. The Takiwasi Addiction Treatment Center (Peru) offers an SUD treatment protocol that parallels this somatic chronic care framework, combining methods from traditional Amazonian medicine and modern psychotherapy.

Amazonian medicine is an ancient indigenous healing system making use of medicinal plants from the Amazon rainforest, according to sophisticated application methods and ritual techniques (Berlowitz et al. 2017; Busmann and Sharon 2006; Luna 1986; Sanz-Biset et al. 2009). Among Amazonian medicinal plants, *Banisteriopsis caapi*, the ayahuasca vine, has become well known in the modern west, and is increasingly discussed for its potentials for assisting the treatment of psychosomatic problems, such as SUD (Bouso and Riba 2014; Fabregas et al. 2010; Labate and Cavnar 2014; McKenna 2004; Riba et al. 2003;

Thomas et al. 2013). Nonetheless, Amazonian medicine offers numerous other plants aside from ayahuasca (Sanz-Biset et al. 2009; Shepard 1998), some of which are being applied at the Takiwasi Center to target symptoms of SUD, such as withdrawal or craving, as part of the addiction treatment program (Berlowitz et al. 2017). Internally generated data from the center suggest favorable results (Giove Nakazawa 2002), but clinical parameters and outcomes have not yet been scientifically established. Consequently, the goal of the current study was to empirically assess the short-term therapeutic effects of this innovative treatment program.

At an early stage of therapeutics evaluation, it is necessary to ask whether an intervention has any benefit at all, rather than testing incremental utilities using comparisons (Donovan et al. 2012). We therefore explored the short-term effects of the Takiwasi treatment by means of a naturalistic design, with a particular focus on (a) addiction severity, (b) substance craving, (c) depressive and anxiety symptoms, and (d) quality of life. Outcome indicators were chosen with reference to international recommendations for the evaluation of addiction treatment effects (Tiffany et al. 2012). We hypothesized a reduction in clinical symptoms (a-c) and an increase in quality of life (d) after treatment completion.

Methods

Participants

Study inclusion criteria consisted of substance dependence diagnosis as per *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR; American Psychiatric Association [APA] 2000) based on the Mini International Neuropsychiatric Interview (MINI; Sheehan et al. 1998), and of the fulfillment of admission criteria to the Takiwasi inpatient treatment (i.e., medical clearance from the center's medical team, Spanish language skills, written motivational statement). Since this research was designed before the DSM-5 release (American Psychiatric Association 2013), we used the prior version of the DSM for the purpose of this study. Data collection was initiated in April 2014 and pre-treatment assessment (T1) was discontinued in June 2016. Post-treatment (T2) data collection carried on until January 2017. From the 68 patient admissions during this time frame, 2 preferred not to participate (personal reasons), 3 did not meet dependence criteria, and 10 entered the study but had incomplete baseline data and were therefore excluded (see Figure 1). The sample at T1 consisted of 53 participants. Since 17 participants dropped out of treatment, the final sample with post-treatment

measures at T2 consisted of 36 participants. The study was conducted according to international regulatory requirements and the Declaration of Helsinki and had been approved by the responsible ethics committee (University of Fribourg, Switzerland).

Study setting

The study was conducted at the facilities of the Takiwasi Addiction Treatment Center in Tarapoto, San Martín Province, Peru. This health-care center offers inpatient treatment (maximum of 18 beds capacity) for individuals with addictive problem. The program is limited to males, due to a Peruvian legal restriction of gender-specificity in this type of residential therapy. In addition, outpatient services are available to both genders and provide assistance for a broad range of mental health problems. The Takiwasi Center has a pioneering character as the world's first accredited, governmentally recognized health institution (Peruvian Health Ministry) applying traditional Amazonian medicine to SUD. It was founded in 1992 by a French medical doctor after a mission with Doctors Without Borders for a primary health-care project (unrelated to addictions) in the Peruvian Andes. Due to the spread of cocaine production sites in the Amazon during the 1980s, there had been a substantial rise in incidence of cocaine and cocaine base paste dependence in the Peruvian San Martín Province (Giove Nakazawa 2002; Sanz-Biset et al. 2009). The Takiwasi Center was created to provide assistance to this situation by making use of local medical resources and Western knowledge about SUD. Today, owing to extensive governmental efforts that supported the cultivation of alternative produce, such as coffee or corn, cocaine production in this area has virtually ceased. The necessity for addiction treatment in the region however remains. The work of the center has become known throughout Peru and beyond its borders, such that it now receives requests by treatment-seekers from around the globe. The clinical staff of the Takiwasi Center is composed of health professionals from both traditional Amazonian and Western medical systems, i.e., specialized traditional healers as well as Western-trained psychologists and physicians, who are operating within a plurimedical and intercultural framework.

SUD treatment protocol

The SUD inpatient treatment at the Takiwasi Center typically lasts between 3 and 12 months, with duration varying according to individual needs. The therapeutic protocol includes both traditional Amazonian treatments and Western psychotherapeutic methods and

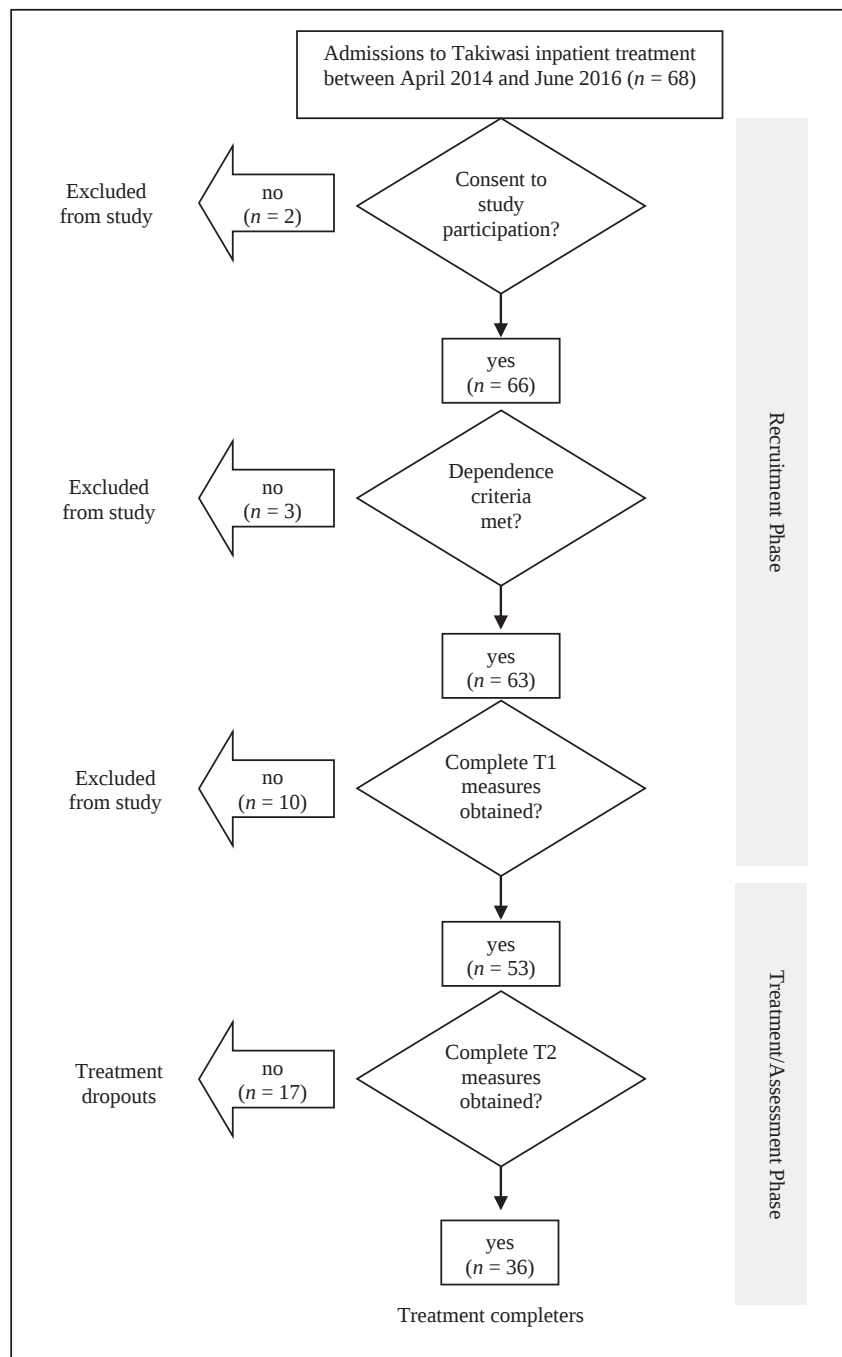


Figure 1. Flow chart illustrating rate of consent to participation, study exclusion/inclusion, and treatment dropout throughout recruitment and assessment.

involves three stages: 1) an initial phase (2–4 weeks) focusing on detoxification; 2) a stage where the therapeutic work deepens and key issues, which often underlie the addictive problem, tend to be addressed; and 3) a final stage in which the person's return to a professional and social life is gradually prepared. All three stages involve the application of both traditional Amazonian and Western therapeutic methods.

Main methods from traditional Amazonian medicine applied at Takiwasi

Amazonian methods for SUD treatment applied at the Takiwasi Center can be grouped into three broad categories, all making use of local medicinal plants in a ritualized context (Berlowitz et al. 2017). First, *purging rituals* use plants with emetic effects that are thought to detoxify the organism, alleviate withdrawal symptoms,

and craving. This technique is applied several times a week in the initial detoxification period, and with a lesser frequency throughout the entire treatment. Second, *dietary forest retreats* are weeklong retreats where patients stay socially secluded in forest huts and are administered medicinal plants by a curandero/a (traditional healer), while adhering to strict nutritional and other behavioral rules. This intervention aims to facilitate emotional processing and self-understanding, as well as to detoxify the client. Dietary forest retreats are prescribed about once every three months, with several weeks of “post-diet” during which certain restrictions still need to be kept. Third, *healing ceremonies* are introduced after an initial detoxification period and are then administered twice a month on average. They involve a ceremonially framed group setting guided by a curandero/a, who administers specific plant medicines, among them also preparations based on the aforementioned ayahuasca plant. These interventions intend to increase awareness of self, of one’s relationship to the world, as well as to cleanse the client from toxins. Plant ceremonies and retreats may involve peak experiences and are believed to help reconcile unresolved emotional trauma, as well as facilitate an increased sense of connection with life, purpose, or meaning.

Main western therapeutic methods applied at Takiwasi

Besides the Amazonian treatments, all patients have weekly psychotherapy sessions with trained psychotherapists, participate in group therapy on a daily basis (e.g., relapse prevention, psychodrama) and occasionally undergo biomedical health checks. They live together in a therapeutic community and perform daily chores guided by an occupational therapist.

Both Amazonian and conventional therapeutic methods are applied simultaneously; however, the specific therapy plan of a given patient is adapted to that person’s clinical necessities.

Measures

Psychiatric diagnoses were assigned using the *MINI* (Ferrando et al. 1998; Sheehan et al. 1998). The *Hospital Anxiety and Depression Scale* (Zigmond and Snaith 1983, HADS; Quintana et al. 2003) was used to assess emotional distress (range 0–42; Cronbach’s alpha .85), consisting of two subscales measuring depression and anxiety (range 0–21; clinical cutoff +8; Bjelland et al. 2002). We measured severity of dependence symptoms with the *Addiction Severity Index 5* (ASI; McLellan et al. 1992), assessing areas of functioning through medical, employment, alcohol use, drug use, legal,

familial/social, and psychiatric composite scores (range 0–1; clinical cutoff scores are available for alcohol use [.17] and drug use [.16]; Rikoon et al. 2006). We used the ASI also for assessing socio-demographic characteristics of participants. The *Craving Experience Questionnaire* frequency form was employed to measure substance craving (CEQ; May et al. 2014). This 10-item questionnaire assesses craving frequency on an 11-point visual analog scale, obtaining averaged scores for total craving (range 0–10; Cronbach’s alpha .94) and three subscales (intensity, imagery, and intrusiveness of craving). Finally, to assess quality of life we used the *World Health Organization Quality of Life-BREF* (WHOQOL-BREF; Lucas-Carrasco 2012, WHOQOL; Group 1998). Its 26 items are answered on a scale from 1 (*very poor*) to 5 (*very good*). Two items are combined to provide an indicator for overall quality of life and health (range 1–5). Four domain scores (range 0–100) are computed out of the remaining 24 items, concerning physical health (7 items; Cronbach’s alpha .78), psychological health (6 items; Cronbach’s alpha .80), social relationships (3 items; Cronbach’s alpha .40¹), and environment (6 items; Cronbach’s alpha .72), with higher scores representing higher quality of life. Change motivation was assessed using the *Readiness to Change Questionnaire* (RCQ; Rodríguez-Martos et al. 2000; Rollnick et al. 1992), with items rated on a scale from –2 (*strongly disagree*) to +2 (*strongly agree*). Motivational stage was assigned on the basis of the highest score among the RCQ stages (pre-contemplation, contemplation, and action).

Procedure

Participants were approached within the first week of admission and informed about the study. Those that agreed to participate wrote an informed consent and completed the battery of socio-demographic and clinical measures for the baseline assessment (T1). The tests related to the main outcome measures (i.e., ASI, HADS, CEQ, WHOQOL-BREF) were re-administered upon treatment completion (T2) within one week (i.e., plus/minus 4 days) of the final treatment day. The average test–retest interval was 215.6 days (SD = 84.7). We have measured post-treatment outcomes in the short term (i.e., in the immediacy of treatment completion), but since the average treatment duration and test–retest interval were extended, the T2 assessment may be argued to reflect medium-term effects with regard to T1.

Data analysis

Statistical analyses were conducted using SPSS 17.0.1 (Statistics for Windows, released 2008, Chicago: SPSS Inc). We performed chi-square and Fisher's exact tests to determine if there were systematic differences among dropouts and treatment completers in the distribution of key categorical variables (i.e., substance type, single vs. poly-substance use, comorbid psychiatric diagnoses, nationality, context of upbringing, marital status, change readiness).

Paired-samples t-tests were used to evaluate differences in the outcome variables between T1 and T2. We tested for the normality of distributions of the pre-post difference scores using the Kolmogorov-Smirnov test. Normally distributed variables included the ASI composite scores' medical status, $D(36) = .10$, $p = .20$; alcohol use, $D(36) = .14$, $p = .06$; drug use, $D(36) = .08$, $p = .20$; familial/social relationships, $D(36) = .08$, $p = .20$; psychiatric status, $D(36) = .10$, $p = .20$; the HADS' overall emotional distress, $D(36) = .20$, $p = .20$; and the WHOQOL-BREF overall quality of life, $D(36) = .13$, $p = .16$. Only for overall substance craving (CEQ), difference scores were significantly non-normal, $D(36) = .15$, $p < .05$. We therefore used the Wilcoxon Signed Rank test for this outcome variable. Significance levels were corrected for multiple comparisons (Bonferroni-corrected [BF] level of significance of $p < .05/8 = .00625$, 2-tailed) since we tested differences on 8 distinct scales. In case of significant differences on the t-test, Cohen's d was calculated as an effect size measure; r was used in the instance of the non-parametric Wilcoxon test.

Results

Sample characteristics

Table 1 displays sociodemographics and clinical features at baseline (T1) for the total initial sample ($n = 53$), for participants who completed the treatment ($n = 36$), and for those that dropped out ($n = 17$). The mean age of treatment completers was 30.86 years ($SD = 8.17$) with an average of 13.07 years of education ($SD = 2.96$). Most completers had never been married (86.1%) and were living with their parents or other relatives (47.2%). Almost 40% of the completers were from Peru. An equal percentage came from other Latin American countries and about 20% came from Europe or North America. A large majority of completers grew up in an urban rather than a rural context (91.7%). Types of substances, for which dependence was diagnosed, involved cannabis (72.2%), alcohol (63.9%), cocaine or cocaine base paste (61.1%), opiates (13.9%), amphetamines and related stimulants (11.1%), and tranquilizers (11.1%). The SUDs of about 80% of the completers

involved several DSM-IV (APA, 2000) diagnoses of dependence and/or abuse simultaneously; only 16.7% used exclusively one substance. Comorbid diagnoses of affective disorders were prevalent among completers (58.3%), as were anxiety disorders (36.1%) and antisocial personality disorder (27.8%). RCQ scores (assessed at T1) placed most completers in the contemplation stage (61.1%) and the rest in the action stage. None were placed in the pre-contemplation stage.

Treatment completion and dropout

About one-third of the initial sample abandoned treatment prematurely (32.08%). The participants who completed the treatment stayed at the center for an average of 217.2 days ($SD = 85.0$). Significance tests for categorical differences between dropouts and completers are displayed in Table 1. Nationality was the only variable that was significantly associated with whether or not treatment was completed ($p < .05$); standardized residuals of the chi-square test indicated the significant difference to reflect an overrepresentation of North American participants amongst dropouts ($se_i = 2.1$).

Treatment effects

Table 2 shows means and standard deviations of the outcome variables and paired-samples t-tests for each outcome variable's main scale. Significant differences on the ASI were found at a BF corrected alpha of .00625 for average drug use ($p < .001$, $d = 1.59$), alcohol use ($p < .001$, $d = 1.21$), psychiatric status ($p < .001$, $d = .91$), as well as social/familial relationships ($p < .001$, $d = 1.44$), all of them being significantly lower after treatment than before. The medical status composite score also decreased from T1 to T2, but the difference was not significant ($p = .317$). There was a significant increase in overall quality of life on the WHOQOL-BREF from T1 to T2 ($p < .001$, $d = .98$). Average emotional distress on the HADS diminished significantly from T1 to T2 ($p < .001$, $d = .97$), as did overall substance craving on the CEQ ($p < .001$, $r = .60$). Figure 2 displays the significant pre-/post-treatment differences found for addiction severity (Figure 2a) and for substance craving, emotional distress, and quality of life (Figure 2b) on the paired samples t-tests.

Discussion

This naturalistic study investigated the short-term therapeutic effects of an alternative SUD treatment which applies a therapeutic protocol combining traditional Amazonian medicine and contemporary psychotherapy. We found significant improvements after treatment for

Table 1. Demographics and clinical features of treatment completers, dropouts, and total initial sample at baseline (T1), and chi-square analyses comparing completers vs. dropouts.

	Total initial sample		Completers		Dropouts		Chi-square analysis	
	N = 53		N = 36		N = 17		χ^2 (df)	p ^b
Age in years, <i>M</i> (<i>SD</i>)	30.05 (7.74)		30.86 (8.17)		28.34 (6.66)			
School education in years, <i>M</i> (<i>SD</i>)	12.86 (2.97)		13.07 (3.04)		12.41 (3.04)			
Male sex %	100		100		100			
Living arrangement %								
With sexual partner/children	18.9		16.7		23.5			
With parents/relatives	47.1		47.2		47.1			
With friends	3.8		5.5		0			
Alone	22.7		25		17.6			
No stable arrangement	7.5		5.6		11.8			
Marital status %								
Married	7.5		11.1		0		2.27(2)	.361
Divorced/separated	3.8		2.8		5.9			
Never married	88.7		86.1		94.1			
Nationality %								
Peruvian	43.4		38.9		52.9		9.50(3)	.027
Latin American (except Peru)	34		38.9		23.5			
European	17		22.2		5.9			
North American	5.6		0		17.7			
Context of upbringing %								
Urban	84.9		91.7		70.6		4.00(1)	.094
Rural	15.1		8.3		29.4			
*MINI diagnoses %								
Substance use disorders	100		100		100			
Affective disorders	62.7		58.3		73.3		1.02(1)	.360
Anxiety disorders	43.1		36.1		60		2.46(1)	.135
Psychotic disorders	5.9		5.6		6.7		.02(1)	1.00
Antisocial pers. disorder	35.3		27.8		53.5		3.03(1)	.112
Dependence diagnosed for %								
2 or more substances	71.7		69.4		76.5		.30(2)	1.00
1 substance + abuse of others	13.2		13.9		11.8			
1 substance only	15.1		16.7		11.8			
Substances dependent on %								
Cannabis	71.7		72.2		70.6		0.02(1)	1.00
Alcohol	54.7		63.9		35.3		3.81(1)	.077
Cocaine	30.2		38.9		11.8			
Cocaine base paste	24.5		22.2		29.4			
Opiates	15.1		13.9		17.6		0.13(1)	.700
Amphetamines/related stimulants	11.3		11.1		11.8		0.01(1)	1.00
Hallucinogens	1.9		0		5.9		2.16(1)	.321
Tranquilizers	15.1		11.1		23.5		1.39(1)	.252
Dominant RCQ stage %								
Precontemplation	1.9		0		5.8		2.71(2)	.268
Contemplation	56.6		61.1		47.1			
Action	41.5		38.9		47.1			

Note. MINI = Mini International Neuropsychiatric Interview; RCQ = Readiness to Change Questionnaire.

^aComorbid diagnoses for 2 participants were missing. ^b p-values for Fisher's exact test.

nearly all outcomes, including the severity of addiction symptoms (drug use, alcohol use, psychiatric status, social/familial relationships), substance craving, emotional distress (anxiety and depressive symptoms), as well as overall quality of life, with large effect sizes. An exception was the somatic medical status of the addiction severity index, which did not significantly change in response to treatment.

Overall, and in accordance with our hypotheses, these results suggest that the long-term, integrative treatment delivered at this center was associated with beneficial

changes in key symptoms of substance dependence. Our results reflect short-term outcomes in relation to the end of the treatment, but medium-term effects with regard to T1 measurement. Our findings are in line with observations by the WHO and others suggesting indigenous medicines to be promising for SUD treatment (Bill et al. 1993; Lu et al. 2009) and with studies reporting positive effects of ayahuasca for SUD (cf. Labate and Cavnar 2014; Nunes et al. 2016). Several large-scale cross-sectional surveys report associations between reduced substance use and ayahuasca applied in varying contexts (Barbosa et al.

Table 2. Dependent-samples t-tests with means and standard deviations of outcome variables.

	Pre-Treatment		Post-Treatment		95% CI of mean difference		t(df)	p
	M	SD	M	SD	Lower	Upper		
ASI composite scores								
Severity of medical status	.26	.27	.21	.21	-.05	.14	1.02(35)	.317
Severity of alcohol use	.38	.28	.06	.10	.22	.40	7.28(35)	p < .0001
Severity of drug use	.26	.12	.06	.06	.16	.24	9.52(35)	p < .0001
Severity of family/social relationships	.49	.19	.26	.15	.17	.28	8.64(35)	p < .0001
Severity of psychiatric status	.44	.21	.21	.17	.14	.31	5.46(35)	p < .0001
CEQ								
Total score (overall craving)	4.73	2.65	1.36	1.38			^a 5.10	p < .0001
Intensity	5.46	2.93	0.99	1.09				
Imagery	4.13	2.96	1.47	1.34				
Intrusion	4.79	2.89	1.60	2.06				
HADS								
Total score (emotional distress)	18.69	7.08	10.56	6.42	5.31	10.97	5.83(35)	p < .0001
Anxiety scale	10.25	4.03	6.67	3.99				
Depression scale	8.44	4.05	3.89	3.39				
WHOQOL								
Overall quality of life	2.58	1.07	3.78	0.93	-1.61	-0.78	-5.87(35)	p < .0001
Physical health domain	47.42	19.35	70.93	18.29				
Psychological domain	43.17	18.21	66.78	16.98				
Social relationships domain	40.05	17.23	56.25	19.76				
Environment domain	52.00	17.25	59.81	13.53				

Note. ASI = Addiction Severity Index; CEQ = Craving Experience Questionnaire; HADS = Hospital Anxiety and Depression Scale; WHOQOL-BREF = World Health Organization Quality of Life-BREF. Higher scores indicate more extreme responses in the direction of the assessed construct for all scales. ^az-score from the Wilcoxon Signed Rank test.

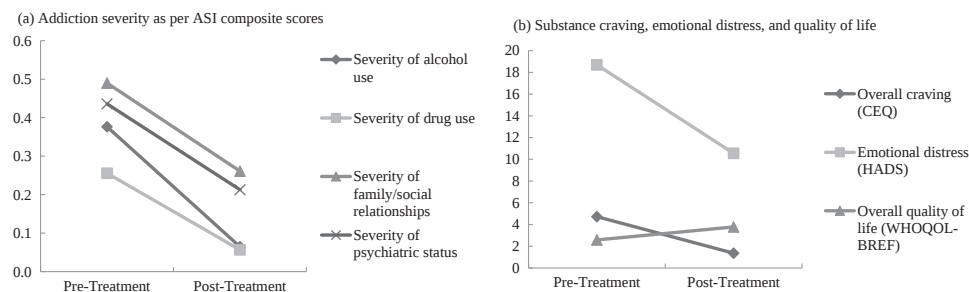


Figure 2. Significant pre-/post-treatment differences.

Significant results of the paired-samples t-tests on the outcome variables. Figure 2(a) displays significant differences on the Addiction Severity Index (ASI) composite scores. ASI scores may range from 0 (no problem) to 1.0 (extremely serious). Figure 2(b) shows significant differences on the Craving Experience Questionnaire (CEQ) in overall craving frequency (from 0 = no craving at all, to 10 = constantly craving the substance), on overall emotional distress (from 0 = none to 24 = severe) of the Hospital Anxiety and Depression Scale (HADS), and on overall quality of life of the World Health Organization Quality of Life-BREF (WHOQOL-BREF) scale (from 1 = very poor, to 5 = very good quality of life). *** $p < .001$ (two-tailed) for all effects, significance at Bonferroni-corrected α of .00625.

2018; Lawn et al. 2017). A small pilot study on patients attending biweekly ayahuasca sessions over 3–9 months in Brazil observed amelioration of psychological factors related to drug dependence (Fernández et al. 2014). Similarly, an observational study reported improvements of problematic substance use indicators in a Canadian aboriginal sample after a brief retreat involving ayahuasca (Thomas et al. 2013). Other studies explore applications in the context of specific SUDs, for instance, crack cocaine dependence (Cruz and Nappo 2018). The Takiwasi treatment, however, consists of a complex blend of methods from traditional Amazonian medicine not limited to ayahuasca, as well as methods from psychotherapy. The associations found in this study may hence not be specifically related to one plant but should be interpreted in light of the intricacies of the overall treatment.

The sample's high prevalence of comorbid affective and anxiety disorders as well as antisocial personality disorder replicates large-scale cross-national findings of SUD patients' most common comorbid psychiatric disorders in general (Merikangas et al. 1998). As our findings demonstrate, in addition to improved SUD-specific symptoms such as urge for consumption, the Takiwasi treatment was also associated with improvements in anxiety and affective states. One potential mechanism within the overall treatment explaining these changes could be the ceremonial usage of ayahuasca. Several studies report antidepressant effects in this context, including a first randomized placebo-controlled trial with clinically depressed patients (Osorio Fde et al. 2015; Palhano-Fontes et al. 2018; Sanches et al. 2016). Studies also report anxiolytic effects of ayahuasca, but evidence is less conclusive (Coe and McKenna 2017; Dos Santos et al. 2016; Santos et al. 2007). Further, a recent study found improvement of emotion dysregulation in a sample with borderline personality traits (Domínguez-Clavé et al. 2018). However, mechanisms other than ayahuasca, such as the Amazonian plants and techniques applied in the scope of dietary retreats and purging rituals, may also support the beneficial changes we found. Indeed, indications from ethnobotanical studies point to other Amazonian plant medicines with relevance for psychological well-being (Sanz-Biset and Canigual 2013, 2011; Shepard 1998). Further, there are early indications for peak experiences, such as the ones that may arise in Amerindian plant ceremonies, to be associated with lasting structural changes, including shifts in personality traits (MacLean, Johnson, and Griffiths 2011). Such changes could be reflected also on a neurobiological level, which could be especially relevant in relation to the aforementioned long-term cerebral adaptations typically observed in SUD patients' brains (Koob and Volkow 2010). Indeed, current neuropharmacological research describes evidence for

certain alkaloids of the ayahuasca brew to play a role in neuroregeneration (Frecska, Bokor, and Winkelman 2016) and hypothesize ayahuasca to facilitate neural architectural changes in the cerebral reward system (Prickett and Liester 2014). Given the complexity and integrative nature of this treatment, individual contributions of the various therapeutic constituents may not be mapped on the basis of our study. Carefully designed randomized placebo-controlled studies could provide complementary information about therapeutic effects of specific methods within this multifaceted integrative treatment.

The lack of significant change we found in the medical composite scores may suggest that the Takiwasi treatment impacts specific psychosocial and consumption-related factors, but does not significantly improve the general somatic health of patients. A large-scale study that compared ASI scores of a general health insurance membership sample ($N = 9,398$) with a clinical sample of insurers with SUD ($N = 327$) reports that, while differences for the other ASI areas were striking, the medical composite scores showed similarity, with the clinical sample's score being only slightly higher (Weisner, McLellan, and Hunkeler 2000). That this measure did not differentiate markedly between clinical and general population in a large scale between-subject design may imply that the medical base rate of SUD patients may be relatively high on a population level and/or that a more elaborate instrument with increased sensitivity would be required to understand the nature of differences in this context.

The finding that there were no individuals in the pre-contemplation stage may be attributed to the Takiwasi admission procedure. Since the Takiwasi treatment demands patients' engagement over a lengthy period of time, it may not be suited for individuals with very low change readiness, which, in turn, may have implications for the transferability of this approach to other settings (where clients in the pre-contemplative stage may not be filtered out).

Dropout in our sample was at a similar level as the generally reported average rate for psychosocial SUD interventions found in a meta-analytic review (35.4%; Dutra et al. 2008). Participants who dropped out of treatment did not significantly differ from completers in any of the tested clinical and socio-demographic measures with the exception that North Americans abandoned treatment more frequently than expected, which may imply a lesser cultural fit of this treatment for people from these geographical regions. However, while it is plausible that specific cultural aspects may have played a role in the increased dropout among North Americans, the number of such participants in the overall sample was small ($n = 3$). This finding could therefore also reflect a sample bias and should be interpreted with caution. A possible reason for

why the increased dropout was observed for North American, but not for European participants, might relate to a higher degree of familiarity of Europeans with the micro-cultural climate at this center, which is influenced by its European founder and the Hispanic context of Peru. Future studies should aim to further explore the patients' cultural profiles in relation to the cultural characteristics of this treatment program and its staff.

This study has a number of limitations. Treatment outcomes were assessed in a naturalistic setting without a comparison group, and outcomes were available only for treatment completers. This design does not allow causal interpretation and limits generalizability. We measured outcomes only in the short term, and sample size was relatively small. The lack of outcome assessment upon participants' return presents a limitation in that the Takiwasi treatment entailed a prolonged period away from a context likely to have been critical in the perpetuation of the pathological substance use. Furthermore, participants were heterogeneous with several comorbidities, however, this is generally representative of substance dependent individuals in residential treatment settings (Chen et al. 2011; Merikangas et al. 1998; Weisner, McLellan, and Hunkeler 2000).

In sum, our findings are preliminary, but indicate multiple positive outcomes and suggest the need for further investigation of this treatment approach. Future studies may build on our findings and extend them to the long term. Whilst the naturalistic research design inevitably had costs, it also had the advantage of capturing synergistic effects arising from the interplay between the various treatment methods, which is considered especially relevant for traditional medical systems (Fønnebo et al. 2007). The loss of synergistic effects is indeed one of the main reasons why, for traditional medicines research, comprehensive paradigms (i.e., whole systems research) are generally preferred to designs that study the various components individually and isolated from the rest of the medical system (Verhoef et al. 2005; World Health Organization 2000). This is to our knowledge the first study empirically assessing the therapeutic effects of this accredited Amazonian medicine-based addiction treatment program, generating novel findings in a field where improved therapeutic means are considered a need on a global level. Our results may aid the development of enhanced SUD therapies combining western treatments with traditional medicines and, in the long term, open new treatment avenues.

Note

1. Due to the small item number in this domain's scale, the indicator for internal consistency may not be reliable (WHOQOL Group 1998).

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Disclosure statement

Dr. Mendive works as scientific coordinator at the Takiwasi Addiction Treatment Center, where the study was conducted.

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