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Within-treatment changes in a novel addiction treatment program using traditional Amazonian medicine

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Abstract

Aims: The therapeutic use of psychedelics is regaining scientific momentum, but similarly psychoactive ethnobotanical substances have a long history of medical (and other) uses in indigenous contexts. Here we aimed to evaluate patient outcomes in a residential addiction treatment center that employs a novel combination of Western and traditional Amazonian methods.

Methods: The study was observational, with repeated measures applied throughout treatment. All tests were administered in the center, which is located in Tarapoto, Peru. Data were collected between 2014 and 2015, and the study sample consisted of 36 male inpatients who were motivated to seek treatment and who entered into treatment voluntarily. Around 58% of the sample was from South America, 28% from Europe, and the remaining 14% from North America. We primarily employed repeated measures on a psychological test battery administered throughout treatment, measuring perceived stress, craving frequency, mental illness symptoms, spiritual well-being, and physical and emotional health. Addiction severity was measured on intake, and neuropsychological performance was assessed in a subsample from intake to at least 2 months into treatment.

Results: Statistically significant and clinically positive changes were found across all repeated measures. These changes appeared early in the treatment and were maintained over time. Significant improvements were also found for neuropsychological functioning.

Conclusion: These results provide evidence for treatment safety in a highly novel addiction treatment setting, while also suggesting positive therapeutic effects.

Keywords: addiction, ayahuasca, safety, Takiwasi, traditional Amazonian medicine

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Introduction

Addiction treatment was an exciting line of inquiry during the first wave of psychedelic research in the mid-20th century, but the field was marred by inadequate research methodology and growing controversies that led to a near total investigatory suspension.[1–4] After a decades-long hiatus, a revitalized second wave is now well underway.[5–7] Once again, addictions are a target of psychedelic research with some impressive early results,[8–14] and there is hope for a breakthrough treatment similar to the recent success of MDMA-assisted psychotherapy for post-traumatic stress disorder.[15] Yet while the psychiatric discovery and embrace of psychedelics is relatively recent, the use of similar substances in shamanic and ethnomedical contexts is much older and is likely to have ancient roots.[16–18]

Therapeutic use of ayahuasca

One such ethnobotanical substance is *ayahuasca*—the common name of the vine *Banisteriopsis caapi*, which contains monoamine oxidase-inhibiting

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β-carbolines and is traditionally used alone or with various admixtures[19,20]—but also the name of the decoction prepared from *B. caapi* and the leaves of a plant containing the psychedelic *N,N*-DMT,[21] such as *Psychotria viridis* or *Diplopterys cabrerana*.[22] Ayahuasca (i.e. the DMT-containing decoction) is powerfully psychoactive but appears to be safe when used appropriately.[23–30] In recent times its therapeutic potential has been increasingly documented, particularly for the alleviation of substance abuse, depression, and anxiety-related disorders.[31–37]

Ayahuasca is not considered to carry a high intrinsic addiction potential,[38,39] and indeed suggestions of anti-addictive outcomes have been reported since the earliest biomedical study on the sacramental use of ayahuasca,[40] with evidence slowly accumulating since then.[41–47] Various potential mechanisms have been proposed,[48–52] yet quantitative studies of ayahuasca for addiction have only rarely been conducted in explicitly therapeutic settings,[53,54] in part due to regulatory challenges.[55]

The Takiwasi Center

Running parallel to these developments is a well-established and nationally accredited therapeutic community in Peru, the Takiwasi Center, which has been employing ayahuasca in the treatment of addictions since 1992[56]—around the same time that human psychedelic research resumed.[57,58] However, Takiwasi is rather poorly characterized as an "ayahuasca-assisted" treatment, since a variety of other traditional techniques are used; for example, the traditional *dieta* (diet) is particularly important, during which a patient enters social seclusion while receiving restricted alimentation, along with the intake of prescribed medicinal plants.[59,60] The ceremonial use of ayahuasca, diets, and other plant-based techniques proceed from traditional Amazonian medicine,[61–63] which Takiwasi combine with Western psychotherapeutic and biomedical approaches.

Being founded by a French medical doctor, the combination of Amazonian and Western medicine in Takiwasi is operated from within a biopsychosocial-spiritual framework.[64] For example, clinical staff at the center may be healers with training in traditional Amazonian medicine, but there are also professional doctors, psychologists, and nurses. Due to potential interactions between pharmaceuticals and plant medicines,[25] patients cease taking psychiatric medications prior to entry, although this does not apply to those with a history of psychosis, as they would not be accepted for treatment.[56] Certain physical health conditions are also part of the center's exclusion criteria, including diabetes, gastric ulcers, and epilepsy, but also renal, cardiac, respiratory or hepatic insufficiency.[56,65] Once admitted, the ideal treatment process lasts around 9 months (although this is flexible), and progresses through stages of: (a) initial isolation (around 8–10 days); (b) main treatment (around 7 months); and finally (c) a reinsertion phase (around 2 months) where patients continue with the main treatment, but are preparing for post-treatment life and thus are able to leave the center and engage in work in the community (see Figure 1). Across the phases, treatment primarily revolves around physical detoxification (focusing on the use of emetic and psychoactive plant preparations), psychotherapy (group and individual), occupational therapy, community living, psychological and spiritual development (through psychoactive plant sessions and diets), and also biomedical evaluation. The application of medicinal plants in Takiwasi has parallels to psychedelic-assisted psychotherapy, although the Takiwasi framework differs in that its roots are in traditional Amazonian medicine. More detailed descriptions of these treatment procedures have been provided by Berlowitz *et al.*,[66] Mabit *et al.*,[67] Bustos,[68] and O'Shaughnessy.[69]

Study rationale

Takiwasi offers the potential for generating unique insights into the use of traditional medicines in addiction treatment, including, but not limited to the use of ayahuasca. Yet while the center's own publications have reported positive patient outcomes,[70] scientific evaluation has been lacking.[71] It is of significance then that results from the first preliminary observational study of Takiwasi's treatment have recently been published,[66] with analyses showing improvements for treatment completers in terms of addiction severity, craving, emotional distress, and quality of life. Comparable results were recently reported in a second observational study,[65] which showed post-treatment improvements in anxiety and depression scores, as well as improved scores on quality of life and spirituality. Although the effect sizes in these studies were large, the end-point analyses used in both studies opened questions about the timing of within-treatment changes, particularly with regard to treatment dropouts that were excluded from analysis. Here we build on these

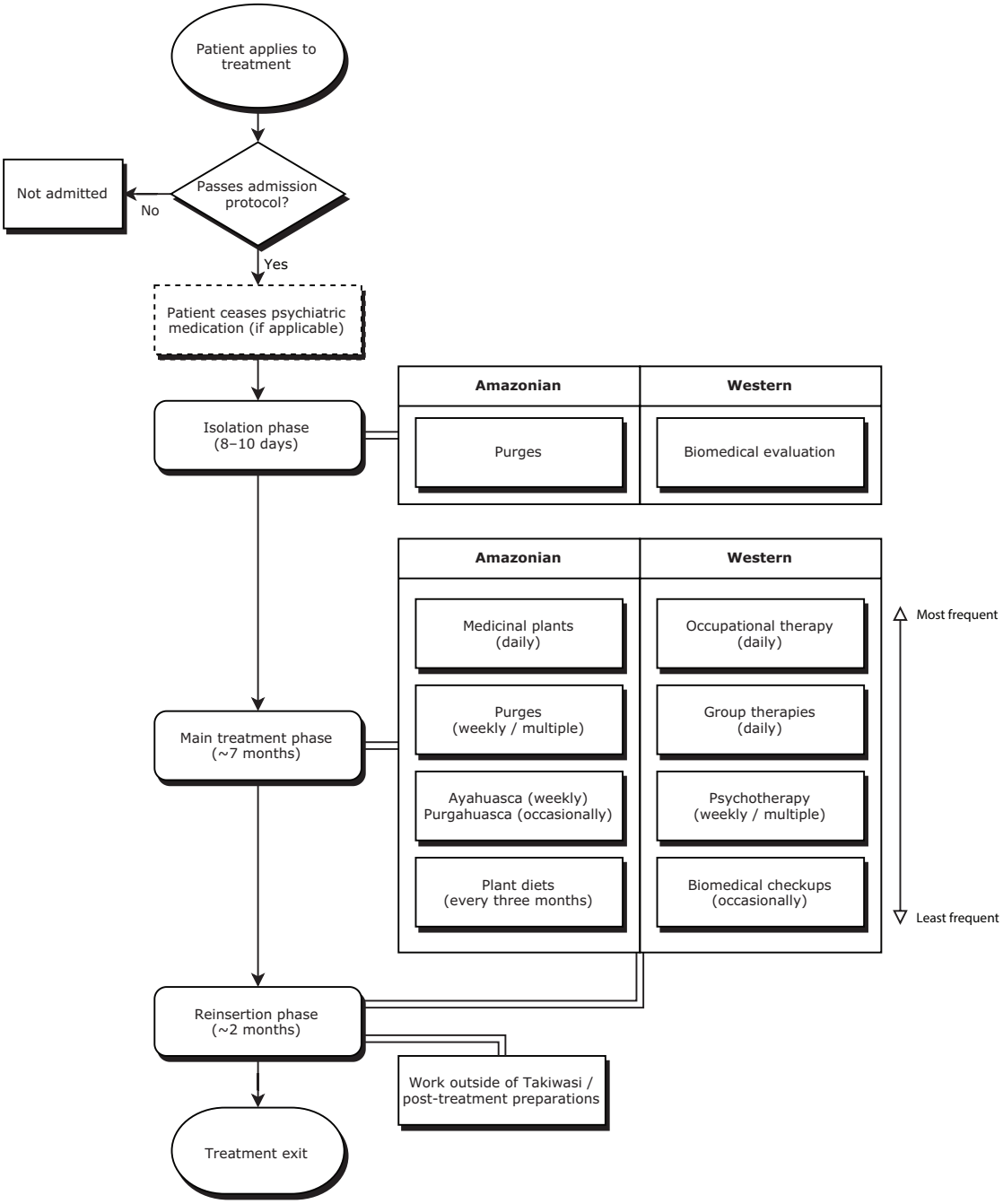

Figure 1. Outline of Takiwasi's treatment regime (average timeline).

results by reporting on patient changes at multiple points within treatment.

Given the clinically and theoretically complex nature of addictions,[72] we attempted to characterize within-treatment change as broadly as possible by following the multi-dimensional addiction recovery model proposed by Dodge *et al.*[73] We thus measured patients on the following domains: (a) physical (somatic health); (b) bio-marker (cortisol, with results to be reported elsewhere); (c) dependency (craving); (d) psychological (stress, mental/emotional well-being, and neuropsychological functioning); (d) psychiatric (mental illness); (e) social (social functioning); and (f) spiritual (spiritual well-being).

Methods

The study was approved by the James Cook University Human Research Ethics Committee (H5267), and all participants gave written informed consent prior to participation. We used the STROBE cohort checklist when writing this report.[74]

Participants

Participation in the study was open to all patients who were: (a) seeking treatment for addiction, and (b) had passed Takiwasi's admission protocol and been admitted as inpatients. Although we did not measure treatment motivation, all patients entered into treatment voluntarily, and previous studies suggest that the majority of Takiwasi patients arrive motivated to seek change.[75] No patients declined to participate in the study. Data were collected from April 2014 to August 2015, and while not all patients completed the full course of treatment, no patients dropped out of the study while in treatment (although study participation ended once a patient had left treatment).

As only male inpatients are admitted to Takiwasi, the final sample consisted of 36 male inpatients with ages on treatment admission ranging from 20 to 50 years ($M = 29$, $SD = 7$), and total time in treatment (from entry to exit) ranging from 3 to 367 days ($M = 183$, $SD = 118$). South Americans made up 58% of the sample, with 28% European, and the remaining 14% North American. Prior to treatment, the most commonly consumed drugs were alcohol (83%), cannabis (71%), and cocaine (51%), with poly-drug use being common (66%). Of the sample, 61% completed the treatment, 22% exited voluntarily (i.e. against staff recommendation), 14% were suspended from treatment, and one patient (3%) abandoned the treatment without advising staff. Further demographics can be found in Table 1.

Design

Similar to Berlowitz *et al.*[66] and in accordance with World Health Organization recommendations for the evaluation of traditional medicines,[76] the overall study design consisted of an observational "black box" view of patient change throughout treatment, which was not intended to isolate specific aspects of the treatment for analysis. We therefore obtained repeated measures on psychological variables in order to assess clinical change in a global sense.

Measures

Addiction severity. The fifth edition of the Addiction Severity Index (ASI)[77,78] is a widely used structured clinical interview that attempts to quantify a patient's addiction severity across seven life problem areas: medical, alcohol, drug, employment, legal, family, and psychiatric. Higher scores indicate greater problem severity for each dimension.

Clinical battery. The clinical battery tests were selected for their relevance in the addiction literature, but also for the suitability of individual test items within a residential treatment context. The measures used were as follows.

Perceived Stress Scale (PSS). The PSS[79,80] was used to measure psychological stress over the previous month. Analyses were made on the 10-item subset (PSS-10), due to its improved psychometric properties.[81] Higher scores indicate greater perceived stress.

Craving Experience Questionnaire–frequency (CEQ-F). The CEQ-F[82] was used to measure the frequency of craving experienced over the past 30 days. Craving is conceptualized in terms of frequency of desire, craving-related imagery, and intrusive thoughts. Higher scores indicate greater frequency of craving over the month prior.

Brief Symptom Inventory (BSI). The BSI[83] was used to assess the prevalence of psychiatric disorder symptoms over the previous 7 days. The test is a shorter 53-item version of the Symptom Checklist-90 Revised,[84] and both instruments measure psychiatric symptoms across nine dimensions. Only results for the Global Severity Index (GSI) are reported here, where higher scores indicate greater overall problem severity.

Spiritual Well-Being Scale (SWBS). The SWBS[85] was used to assess two dimensions at the time of testing: Religious Well-Being (RWB) and Existential Well-Being (EWB). RWB items explicitly address religious and spiritual notions of God, whereas EWB items are secular and probe life satisfaction and meaning. On both dimensions, higher scores indicate greater well-being.

Short Form Health Survey 36 version 2 (SF-36v2). The SF-36v2[86] was used to capture perceived changes in health over the past 4 weeks. While the SF-36v2 measures eight health domains, we only report here the global measures

of: (a) physical health (Physical Component Summary; PCS), and (b) mental/emotional health (Mental Component Summary; MCS). For both domains, higher scores indicate better health.

Self-Evaluated Transition (SET). The SET is a single 5-choice item from the SF-36v2 that captures perceived change in general health over the past year. The patient rates their current "health in general" compared with 1 year prior as either: 1 (*much better*), 2 (*somewhat better*), 3 (*about the same*), 4 (*somewhat worse*), or 5 (*much worse*).

Neuropsychological functioning. The Repeated Battery for the Assessment of Neuropsychological Functioning Update (RBANS)[87] was used to test for abnormal cognitive functioning. With two equivalent testing forms, the Spanish version allows for a single retest only. The instrument assesses performance through 12 subtests that comprise five indexes: immediate memory, visuospatial, language, attention, and delayed memory. For all indexes, higher scores indicate better performance (with low scores relative to age bracketed norms suggesting cognitive impairment).

Procedures

Addiction severity. The ASI was administered to patients on intake only, most often by a co-author of this work (I.B.), but at times by Takiwasi staff instead. It was administered on average 2 days into treatment ($SD = 3$ days).

Clinical battery. Measurements on the clinical battery were made at important treatment points that we termed *milestones*. In consultation with Takiwasi staff, the selected milestones were: (a) treatment admission, (b) approximately 1 month after each diet, and (c) exit from treatment (although it should be noted that in practice treatment exit could occur at any point for a variety of reasons). There were five milestones in total, herein designated M_1–M_5.

Dieting provided a natural measurement point in treatment, since it occurs with some regularity (around every 2–3 months) and marks a consolidation point for patients within the treatment. Moreover, the diets are followed by a reflective phase where patient plant intake is negligible, which allowed us to minimize interference from the acute effects of psychoactive plants when taking repeated measures. From M_1 to M_5, the sample sizes were 22, 19, 18, 13, and 9,

Table 1. Patient demographics.

	Percentage of the study sample[a]
Country of residence	
Peru	33
Rest of South America	25
France	17
Rest of Europe	11
North/Central America	14
Age (on admission)	
20–29	58
30–39	31
40–49	8
>49	3
Religion (on admission)	
None	50
Christian	39
Buddhist	5
Islamic	3
Other	3
Drug use 30 days prior to treatment[b]	
Alcohol	83
Cannabis	71
Cocaine and derivatives	51
Sedatives	26
Opiates	23
Amphetamines	20
Barbiturates	13
Hallucinogens	9
Poly-drug use	66
Total time spent in treatment	
<1 month	17
1–3 months	11
4–6 months	17
7–9 months	17
>9 months	38
Treatment exit	
Completed	61
Voluntary	22
Suspended[c]	14
Abandoned	3

[a] $N = 36$.
[b] Drug use subcategories are not mutually exclusive.
[c] Three patients were suspended for leaving the center and consuming alcohol and cocaine.

respectively ($N = 36$). The average number of days in treatment (with standard deviations) for patients at M_1–M_5 were: 3 (3), 110 (31), 169 (31), 245 (30), and 309 (27).

Neuropsychological functioning. The RBANS was administered on treatment intake, and at a follow-up point either at the end of treatment, or at least 2 months into treatment ($n = 8$). The average number of days in treatment before the second administration was 153 ($SD = 70$). Given the language-dependent nature of some test sections, the RBANS was only administered to fluent Spanish speakers.

Analyses. All analyses were conducted using R.[88] Effect sizes for *t*-tests were calculated with *effsize*.[89] Mixed-effects models were generated using *lme4*,[90] with significance values from *lmerTest* using Satterthwaite's method.[91,92]

Intake comparisons. For group analysis we compared the sample's intake ASI scores with normative values from mainstream inpatient centers. Due to the cultural diversity of Takiwasi's patients and the lack of global ASI normative data, these comparisons were unavoidably cross-cultural. One-sample *t*-tests were used to check for significant differences. We also compared Takiwasi patients' intake scores (M_1) on the clinical battery against available normative samples using one-sample *t*-tests.

Within-treatment changes. We analyzed the clinical battery in terms of predicted change over time from M_1 versus M_2–M_5 (plotted against normative values for comparative purposes). Mixed-effects models were used to maximize the data available for analysis (i.e. we included all data points in the analyses, irrespective of a patient's time in treatment at study enrollment, or reason for treatment exit), and also to account for the lack of statistical independence due to repeated measures.[93] In all models the fixed effect was treatment milestone (categorical), with patient as the random effect. All models were random intercept only, and thus implied the modeling assumption of an invariant effect of time spent in treatment across patients. Since treatment milestone was a proxy for time spent in treatment, we also tested the models with the addition of total treatment time (in days) as a predictor, but its addition was not warranted based on Akaike information criterion (AIC) values.

For neuropsychological functioning, we compared intake and within-treatment performance using paired-samples *t*-tests, using Hedges'[94] correction for Cohen's *d* as the effect size.

Dropout analysis. We compared early treatment dropouts (i.e. those who spent less than 30 days in treatment) against the rest of the sample via a logistic regression, using demographics and ASI intake scores as predictors, and a binary "dropout" variable as the outcome.

Results

Intake profile

We first characterize the Takiwasi sample on intake, making comparisons against available normative values.

Addiction severity. Figure 2 shows ASI composite score means and standard errors for the Takiwasi sample ($n = 34$; ASI data were unavailable for two patients), Canadian addiction patients being readmitted to treatment with at least three previous attempts (sample sizes range from 517 to 1474),[95] and USA addiction inpatients ($N = 3133$).[77]

Compared with the Canadian sample, Takiwasi patients had significantly higher scores on (a) drug, $t(33) = 3.00$, $p < 0.01$, Cohen's $d = 0.51$, 95% CI for d (−0.19, 1.22); (b) family, $t(33) = 3.06$, $p < 0.01$, $d = 0.53$, CI (−0.18, 1.24); and (c) legal, $t(33) = 3.03$, $p < 0.01$, $d = 0.52$, CI (−0.19, 1.23). Significantly lower scores for Takiwasi patients were found for (a) medical, $t(33) = -3.08$, $p < 0.01$, $d = -0.53$, CI (−1.24, 0.18); and (b) work $t(33) = -2.33$, $p = 0.026$, $d = -0.40$, CI (−1.10, 0.31).

When compared with the US sample, Takiwasi patients had significantly higher scores for (a) drug, $t(33) = 5.99$, $p < 0.001$, $d = 1.03$, 95% CI for d (0.28, 1.77); (b) family, $t(33) = 7.11$, $p < 0.001$, $d = 1.22$, CI (0.46, 1.98); and (c) psychiatric, $t(33) = 5.28$, $p < 0.001$, $d = 0.91$, CI (0.17, 1.64).

Clinical battery. For the intake sample ($n = 22$; except for CEQ, $n = 27$), we first made comparisons where non-clinical norms were available. We found that (a) PCS scores were not significantly different from the US average ($N = 4024$)[96]: $t(21) = -1.23$, $p = 0.233$, Cohen's $d = -0.26$, 95% CI for d (−1.15, 0.63); (b) MCS scores were

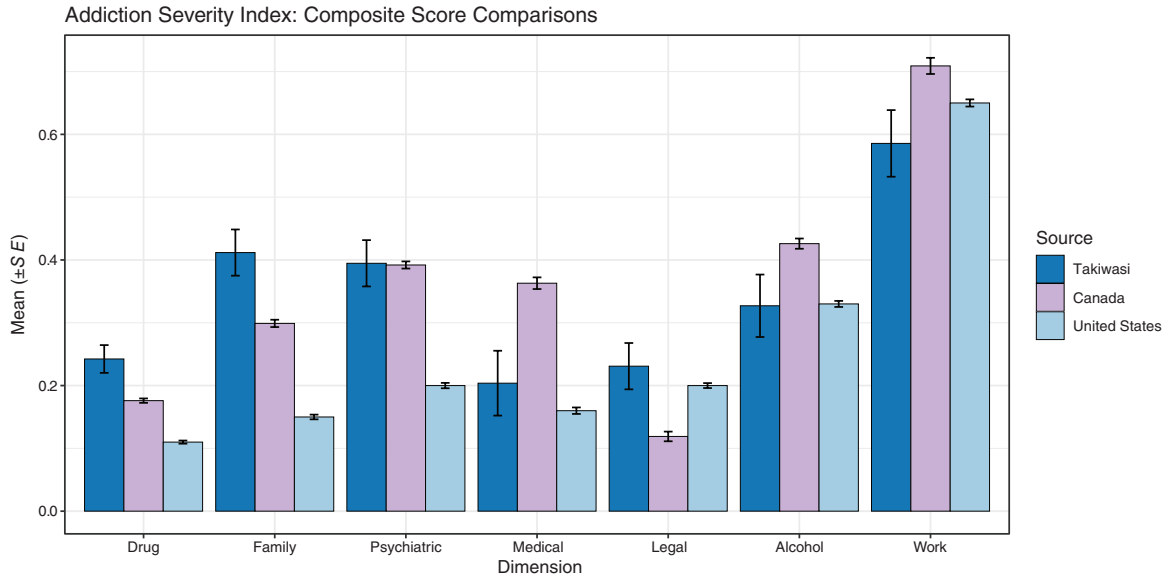

Figure 2. ASI samples and normative comparisons.

significantly lower than the US average ($N=4024$)[96]: $t(21)=-9.47$, $p<0.001$, $d=-2.02$, CI (−3.11, −0.93); (c) PSS-10 scores were significantly higher than the US male average ($N=968$)[97]: $t(21)=8.59$, $p<0.001$, $d=1.83$, CI (0.78, 2.89); and finally (d) GSI scores were significantly higher than non-clinical US males ($N=361$)[98]: $t(21)=8.13$, $p<0.001$, $d=1.73$, CI (0.69, 2.77).

For those measures where only clinical comparisons were available, we found that (a) RWB scores were possibly lower than US mental health patients ($N=182$)[99]: $t(21)=-2.21$, $p=0.038$, $d=-0.47$, 95% CI for d (−1.37, 0.43); (b) EWB scores were not significantly different from US mental health patients ($N=182$)[99]: $t(21)=-0.41$, $p=0.686$, $d=-0.09$, CI (−0.97, 0.80); and (c) CEQ-F scores were significantly higher than an Australian sample of alcohol abuse outpatients ($N=276$)[82]: $t(26)=4.01$, $p<0.001$, $d=0.77$, CI (−0.05, 1.59).

Within-treatment changes

Clinical battery. Here we present predictive mixed-effects models for patient change throughout treatment on the clinical battery, where each estimate is relative to M_1, plotted alongside norms from the sources previously mentioned in the intake analyses. Figure 3 shows model estimates for those tests where higher scores indicate *positive* clinical outcomes. Estimates are significant at $p<0.001$, except for RWB: M_2 ($p<0.01$), M_4 ($p<0.01$), M_5 ($p=0.05$); and PCS: M_2 ($p<0.01$), M_3 ($p=0.023$), M_4 ($p=0.026$), M_5 ($p<0.01$).

Figure 4 shows model estimates for those tests where higher scores indicate *negative* clinical outcomes. All estimates are significant at $p<0.001$, except for GSI M_3 ($p<0.01$). Estimate confidence intervals for both positive and negatively grouped tests can be found in Tables 2 and 3.

Self-evaluated transition. Figure 5 shows response percentages for the SET item, comparing health transition on intake (M_1; $n=22$) versus repeated measures during treatment (M_2–M_5; $n=28$, with 59 administrations total). Excluding intake, no patients in treatment ever rated their health as "somewhat worse" or "much worse," and there were only two that ever rated their health as "about the same."

Neuropsychological functioning. Mean score increases from intake to treatment for the group ($n=8$) were found for all indexes. However, paired-samples t-tests for treatment versus intake scores were only significant for Total Scale, $t(7)=3.37$, $p=0.012$, $g=0.55$, 95% CI for g (0.17, 0.92); and Delayed Memory, $t(7)=2.73$, $p=0.029$, $g=0.74$, CI (0.08, 1.40). Complete index comparisons can be found in Table 4.

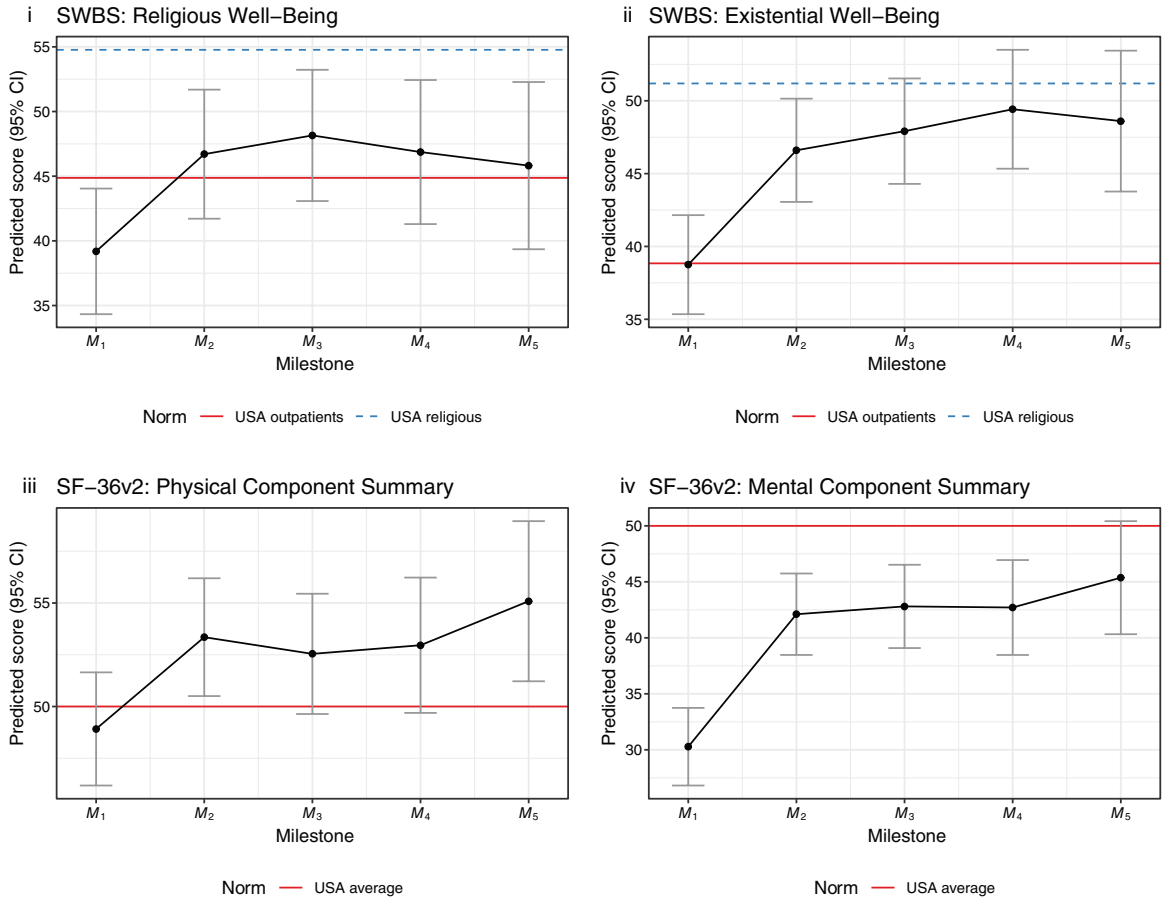

Figure 3. Mixed-effects model estimates (positive grouping).

Dropout analysis

Logistic regression analyses showed no significant relationships between early treatment dropouts (i.e. those who spent less than 30 days in treatment; $n = 6$) and the rest of the sample ($n = 30$) for either nationality, religion, or ASI intake scores (for all dimensions). However, patient age at treatment admission was significant, and for simplicity we report *t*-test results for age between the two samples: Early treatment dropouts were younger ($M = 22$ years, $SD = 2$) than the rest of the sample ($M = 30$ years, $SD = 7$), $t(26) = -5.24$, $p < 0.001$, Cohen's $d = -1.24$, 95% CI for d $(-2.17, -0.30)$.

Discussion

Takiwasi patients on admission

Our results indicate that Takiwasi patients can be expected to have a high severity of addiction on intake, with ASI elevations at least on drug and family problems in comparison to mainstream centers. Based on ASI psychiatric cutoff scores,[100] Takiwasi patients are also likely to have psychiatric co-morbidity on admission, a finding supported by intake GSI elevations, and also recent results from Berlowitz *et al.*[75] where affective and anxiety disorders were found to be prevalent. Overall, the Takiwasi patients' addiction severity profile was comparable to the most severe Canadian readmission sample reported by Simoneau and Brochu,[95] where patients with higher problem severity were re-seeking treatment after at least three prior admissions. However, medical problems in the Takiwasi sample were less severe than the Canadian sample, being more comparable in that domain to the US inpatient average.

The intake profile on the clinical battery supported the ASI findings, and portrayed patients that are likely to be highly stressed, suffering from mental illness symptoms, and experiencing frequent craving. Mental and emotional health is likely to be especially low, although we did not find evidence that physical health is low on average. Religious

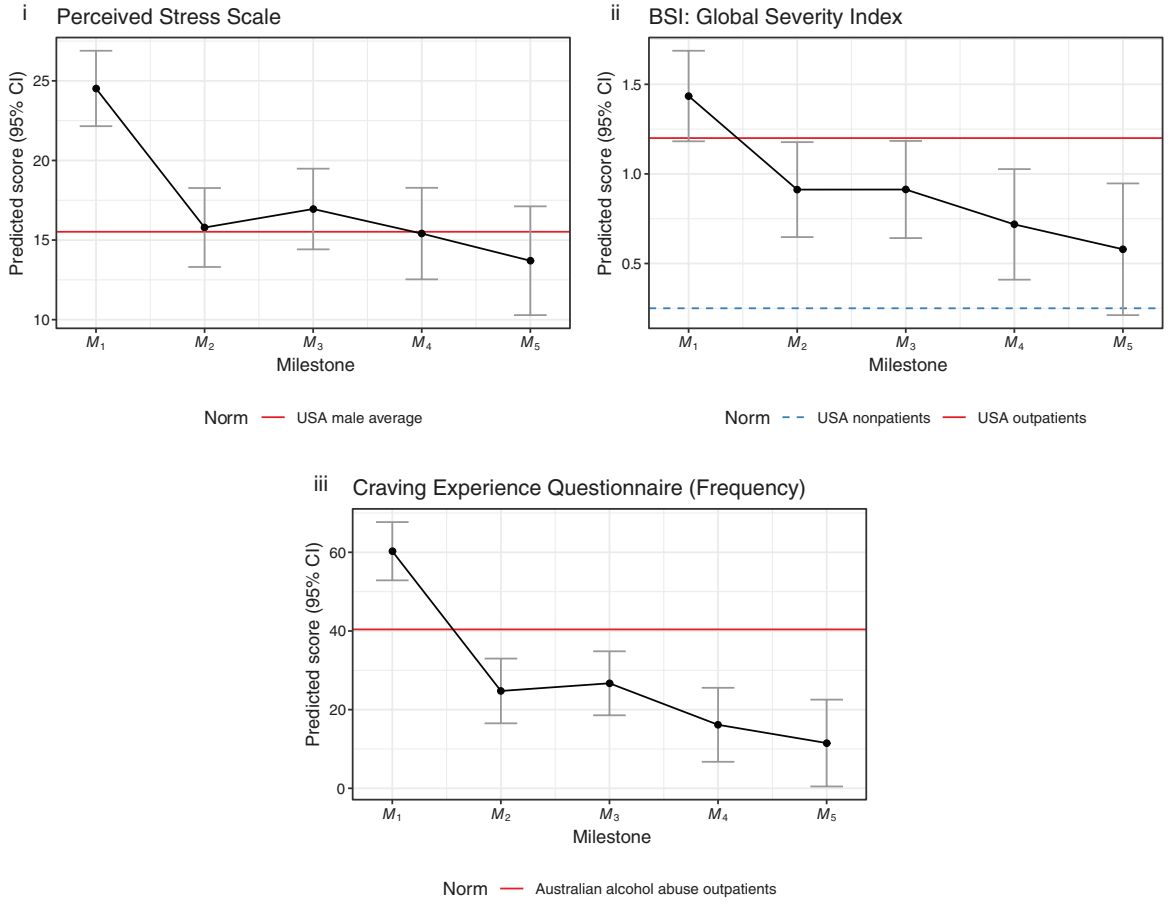

Figure 4. Mixed-effects model estimates (negative grouping).

Table 2. Confidence intervals for model estimates (positive grouping).

Scale	95% CIs for model estimates (by milestone)				
	Intake	Change versus intake			
	M_1	M_2	M_3	M_4	M_5
SWBS					
RWB	[34.5, 43.9]	[3.3, 11.7]	[4.4, 13.5]	[2.5, 12.9]	[0.3, 13.0]
EWB	[35.5, 42.1]	[4.4, 11.3]	[5.4, 12.9]	[6.4, 15.0]	[4.7, 15.0]
SF-36v2					
PCS	[46.3, 51.6]	[1.7, 7.2]	[0.6, 6.7]	[0.6, 7.5]	[2.0, 10.3]
MCS	[26.9, 33.6]	[8.0, 15.6]	[8.5, 16.6]	[7.8, 17.0]	[9.5, 20.7]

CI, confidence interval; EWB, Existential Well-Being; MCS, Mental Component Summary; M_n, treatment milestone; PCS, Physical Component Summary; RWB, Religious Well-Being; SF-36v2, Short Form Health Survey 36 version 2; SWBS, Spiritual Well-Being Scale.
Significance values. $p < 0.001$ for all estimates except as noted. RWB: M_2 ($p < 0.01$), M_4 ($p < 0.01$), M_5 ($p = 0.05$).
PCS: M_2 ($p < 0.01$), M_3 ($p = 0.023$), M_4 ($p = 0.026$), M_5 ($p < 0.01$).

Table 3. Confidence intervals for model estimates (negative grouping).

Scale	95% CIs for model estimates (by milestone)				
	Intake	Change versus intake			
	M_1	M_2	M_3	M_4	M_5
PSS-10	[22.2, 26.8]	[−11.2, −6.2]	[−10.3, −4.9]	[−12.2, −6.0]	[−14.5, −7.1]
GSI	[1.2, 1.7]	[−0.8, −0.2]	[−0.8, −0.2]	[−1.1, −0.4]	[−1.3, −0.5]
CEQ-F	[53.0, 67.5]	[−43.0, −28.1]	[−41.5, −25.8]	[−53.4, −34.9]	[−59.8, −37.7]

CEQ-F, Craving Experience Questionnaire (frequency); CI, confidence interval; GSI, Global Severity Index; M_n, treatment milestone; PSS-10, Perceived Stress Scale (10-item version).
Significance values. $p < 0.001$ for all estimates except for GSI M_3 ($p < 0.01$).

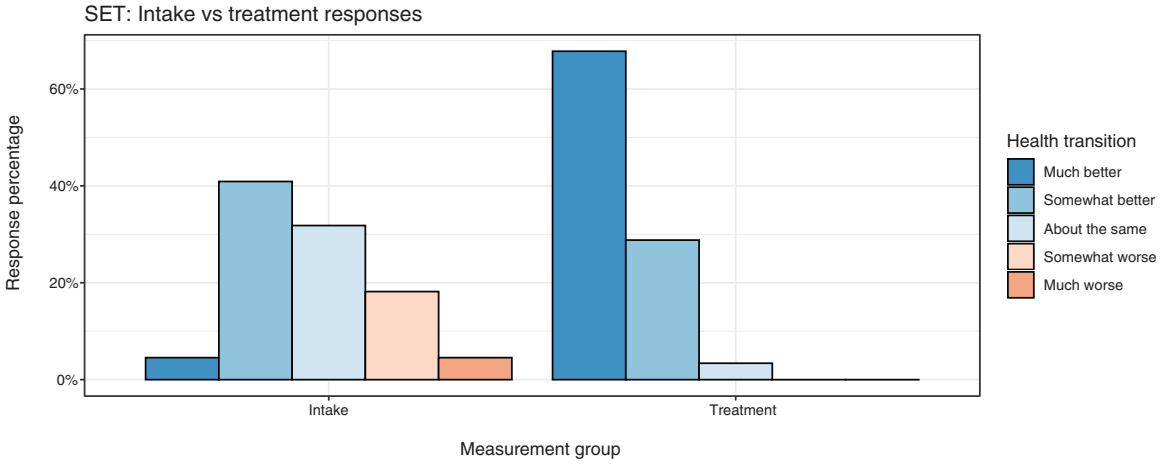

Figure 5. SF-36v2: Self-evaluated transition.

and existential well-being were comparable to US clinical populations, and cognitive functioning may be in the "low average" range.[87]

Within-treatment changes

Over the course of treatment, we find that Takiwasi patients are likely to make clinically significant improvements on a variety of measures relevant to addiction. Specifically, patients are predicted to see strong increases in mental and emotional health, in addition to increased meaning and purpose in life. Large reductions in perceived stress, mental illness symptoms, and craving can also be expected. The most dramatic shifts appeared earlier in the treatment, and these changes seem to be at least maintained over time (if not further improved), although we had limited statistical power to assess later stage changes. Although Berlowitz *et al.*[66] found that Takiwasi treatment completers had large and clinically significant improvements on nearly all measures, no significant changes in physical health were found. However, as the authors note, ASI medical composite scores may not be sufficiently sensitive for this purpose. Our application of the SF-36v2 supported this interpretation, as the physical health models suggested a general improvement in health that was maintained over the course of treatment. Additionally, self-reported health transitions were nearly universally positive for all measurement points beyond intake. Cognitive functioning provided further evidence for improvement, which was most notable in the domain of delayed memory.[23]

While our results accord with the end-point analyses of Berlowitz *et al.*[66] and Giovannetti *et al.*,[65] here we increased the temporal resolution of within-treatment measurement, finding that clinical improvements occur relatively quickly

Table 4. RBANS: intake versus treatment.

Index	Intake[a]		Treatment[a]				
	M	*SD*	*M*	*SD*	Change	95% CI[b]	*g*
Total Scale	82.9	12.4	90.2	10.9	7.4*	[2.2, 12.5]	0.55
I. Memory	84.6	13.8	89.9	16.1	5.2	[–0.5, 11.0]	0.29
Visuospatial	83.8	11.4	86.1	11.9	2.4	[–4.9, 9.7]	0.18
Language	96.1	7.3	101.8	7.7	5.6	[–3.8, 15.0]	0.67
Attention	88.0	18.5	92.8	13.4	4.8	[–1.6, 11.1]	0.20
D. Memory	82.9	15.4	94.5	8.6	11.6*	[1.6, 21.7]	0.74

[a]$n = 8$.
[b]Confidence interval for mean change from intake to treatment.
**Significance values*. Total Scale: $p = 0.012$. Delayed Memory: $p = 0.029$. All others: $p > 0.05$.

(compared with the length of the full treatment), suggesting that dropouts roughly beyond the third month are unlikely to be caused by lack of clinical change. However, our results did suggest that younger patients may be more likely to drop out of treatment early on. Further investigations of patient change within the opening months of treatment appear to be warranted.

Finally, we found some divergence in the modeling of spiritual well-being throughout treatment. Takiwasi's treatment regime is complex, and spirituality and religion play multifaceted roles within it. Psychedelics are known to induce altered states of consciousness of a "mystical" type[101–103] with potentially profound implications,[104,105] and ayahuasca can be similarly potent.[106,107] It is interesting then to note the differences that we observed for Takiwasi patients, with strong predicted increases in existential well-being (perhaps even toward levels seen in US religious samples), whereas spiritual well-being formulated in explicitly religious terms was more uncertain. This contrast possibly reflects pre-existing differences in religiosity (e.g. 50% of the sample were non-religious on admission), but also suggests differences for patients in coming to terms with the apparent spiritual content of ayahuasca and other plant ceremonies.[108]

Limitations and significance

Our observational study design precludes the causal attribution of patient change to particular aspects of the treatment, although the use of ayahuasca gives an obvious and empirically supported target for treatment effects.[34,46] Importantly however, the design does not distinguish between specific treatment interventions and the unusual environment of a residential center: Other variables such as the passage of time, the potential development of community and friendships within treatment, the lack of access to drugs of abuse, and the removal of patients from their daily life circumstances would all be probable contributing factors to changes seen within treatment. On the other hand, it is worth noting that many of the treatment processes are demanding (e.g. many of the plants utilized in Takiwasi induce emesis), and they are unlikely to be considered at all pleasant by patients. In this sense it is impressive that patients with serious addiction problems continue with the treatment for as long as they often do.

Despite the above limitations, the uniformity of the present results would be surprising if the effects of the treatment were broadly deleterious. Thus at a minimum, we provide evidence of treatment safety in a highly novel setting. However, while ayahuasca is known to have an acceptable safety profile from a pharmacological perspective,[26,34,109] many of the Amazonian techniques used in Takiwasi are not yet well studied scientifically, despite indigenous and community usage of the same plants in medical and other contexts.[59,63,110,111] Thus although Takiwasi's exclusion criteria,[56,65] biomedical evaluation, and practitioner expertise likely increase the safety margin—particularly for international and urban patients where interactions not seen in traditional settings increase in likelihood (e.g. pharmaceutical interactions)—further study is needed on the basic effects of Amazonian medicinal plants and practices.

Our results also strongly suggest a therapeutic effect, but we cannot yet determine if these patient changes translate into addiction treatment success. Linking our findings to treatment effectiveness would require longitudinal studies that follow-up on patients once they return to their communities, where there are likely to be more opportunities for relapse. Moreover, it is difficult to assess how well these results would generalize to other patients seeking treatment, given that the Takiwasi admission protocol filters out those who are not yet motivated to commit to treatment,[66] implying that the treatment may be suited to certain patient profiles.[75] Yet irrespective of the admission protocol, it seems unlikely that patients who are not ready to change would stand to benefit from this approach, especially considering the difficult nature of the treatment. However, given the cultural diversity and relatively severe addiction profile of the sample, our results do suggest that this mode of treatment may hold promise in those areas where conventional treatment approaches are failing.

Overall, our findings are consistent with the contemporary literature on the use of indigenous psychoactive plant sacraments,[34,37,39,40,47,54,112,117] and the use of classical hallucinogens more generally.[9,12,36,41,118–126] However, the present results should not be associated with the use of ayahuasca alone, especially considering that it forms one element in a complicated treatment protocol (see Figure 1). For example, when asked to select the most important aspects of the treatment, Takiwasi healers in fact most frequently chose dietary retreats, even though ayahuasca ceremonies were also considered to be important.[64,127–130] Moreover, the focus on medicinal plants and emesis may be connected to effects in the gut–brain axis,[131] which has recently been linked with opioid dependence.

Conclusion

The resurgence of psychedelic research holds promise for the addiction treatment field, and Takiwasi provides a unique parallel to these developments, by now carrying decades of clinical experience. Takiwasi's treatment protocol is more deeply connected with traditional medical practices, and while such an approach may have its own benefits and be more (or less) appropriate for specific populations, further clinical work is called for in order to investigate treatment effectiveness. Qualitative work may also be helpful not only in providing converging lines of evidence for treatment effects and potential mechanisms, but for further delineating the nature of the treatment itself, particularly in relation to concepts of health, illness, and safety, and how they relate to the re-emerging field of psychedelic medicine.

Author contributions

David M. O'Shaughnessy: Conceptualization, Methodology, Investigation, Formal analysis, Funding acquisition, Writing—Original draft.

Ilana Berlowitz: Investigation, Writing—Review & editing.

Robin Rodd: Supervision, Writing—Review & editing.

Zoltán Sarnyai: Supervision, Writing—Review & editing.

Frances Quirk: Supervision, Funding acquisition, Writing—Review & editing.

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Conflict of interest statement

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