Received: 15 April 2022 | Accepted: 18 November 2022

DOI: 10.1111/add.16115

RESEARCH REPORT

ADDICTION SSA

Long-term recovery from opioid use disorder: recovery subgroups, transition states and their association with substance use, treatment and quality of life

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Funding information
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Abstract

Background and Aims: Limited information exists regarding individual subgroups of recovery from opioid use disorder (OUD) following treatment and how these subgroups may relate to recovery trajectories. We used multi-dimensional criteria to identify OUD recovery subgroups and longitudinal transitions across subgroups.

Design, Setting and Participants: In a national longitudinal observational study in the United States, individuals who previously participated in a clinical trial for subcutaneous buprenorphine injections for treatment of OUD were enrolled and followed for an average of 4.2 years after participation in the clinical trial.

Measurements: We identified recovery subgroups based on psychosocial outcomes including depression, opioid withdrawal and pain. We compared opioid use, treatment utilization and quality of life among these subgroups.

Findings: Three dimensions of the recovery process were identified: depression, opioid withdrawal and pain. Using these three dimensions, participants were classified into four recovery subgroups: high-functioning (minimal depression, mild withdrawal and no/mild pain), pain/physical health (minimal depression, mild withdrawal and moderate pain), depression (moderate depression, mild withdrawal and mild/moderate pain) and low-functioning (moderate/severe withdrawal, moderate depression and moderate/severe pain). Significant differences among subgroups were observed for DSM-5 criteria ($P < 0.001$) and remission status ($P < 0.001$), as well as with opioid use ($P < 0.001$), treatment utilization ($P < 0.001$) and quality of life domains (physical health, psychological, environment and social relationships; Ps < 0.001, Cohen's fs ≥ 0.62). Recovery subgroup assignments were dynamic, with individuals transitioning across subgroups during the observational period. Moreover, the initial recovery subgroup assignment was minimally predictive of long-term outcomes.

William H. Craft and Hwasoo Shin contributed equally to this study.

Conclusions: There appear to be four distinct subgroups among individuals in recovery from OUD. Recovery subgroup assignments are dynamic and predictive of contemporaneous, but not long-term, substance use, substance use treatment utilization or quality of life outcomes.

KEYWORDS
MOUD, opioid use disorder, personalized medicine, psychosocial factors, quality of life, recovery, recovery dimensions, recovery trajectories, subgroup, treatment

INTRODUCTION

Opioid use disorder (OUD) remains a key challenge to public health in the United States. In the 12-month period ending May 2021, 73 203 individuals died of an opioid overdose, a 46.8% increase relative to 2019 [1]. The societal costs of the OUD epidemic are monumental, with a study estimating the total economic cost at $1.02 trillion in 2017 alone [2]. Nonetheless, results of a study published in 2020 reported that 1.2 million individuals were estimated to be in recovery from OUD [3] and efficacious treatment options are available.

Recovery from substance use disorder is a multi-dimensional process that includes factors beyond abstinence, such as quality of life, employment and social relationships. Descriptive short-term outcomes (i.e. 1 year or less) [4–7] and longer-term assessments (i.e. greater than 5 years) [8–11] following OUD treatment have been reported, although they have not identified psychosocial subgroups of, nor trajectories across, the multi-dimensional recovery process. However, a personalized treatment approach that recognizes (a) the existence of distinct subgroups and (b) individual trajectories across these subgroups over time is necessary to characterize, understand and support a successful recovery. Subgroup differentiation may be accomplished by synthesizing the multi-dimensional recovery process into latent constructs. Such subgroups have been identified in alcohol use disorder [12]. However, to our knowledge, such analyses have never been conducted among individuals in OUD recovery over the longer term.

To this end, we performed an analysis of individuals in recovery from OUD. Through a data-driven machine learning approach, we (1) identified dimensions of OUD recovery based on psychosocial and opioid dependence variables; (2) used these dimensions to classify individuals into distinct recovery subgroups; (3) validated these subgroups by testing for associations with diagnostic criteria and important health outcomes including opioid misuse, treatment utilization and quality of life measures; and (4) explored the dynamic nature of subgroup assignments over time to understand individual recovery trajectories. To accomplish these aims, we examined data from individuals that completed a 24-month observational study following participation in a clinical trial of long-acting subcutaneous buprenorphine. In addition, to examine long-term outcomes we recruited from the entire initial sample of participants to obtain data at approximately 4 years post-clinical trials.

METHODS

Participants

Participants were individuals with OUD who received long-acting subcutaneous buprenorphine injections (BUP-XR) as part of a randomized clinical efficacy study (NCT0235790) and/or open-label safety study (NCT02510014) and compassionate use extension study (NCT02896296), and then enrolled in the Remission from Chronic Opioid Use-Studying Environmental and SocioEconomic Factors on Recovery (RECOVER, NCT03604861) Study. RECOVER assessed changes in clinical, socio-economic, psychosocial, substance use and treatment outcomes across five time-points (baseline, 6, 12, 18 and 24 months). The Kessler's Psychological Distress (K6) was added after the start of the RECOVER study in order to evaluate psychological distress and anxiety. RECOVER participants were then contacted for a long-term follow-up assessment (NCT04577144), which assessed all the measures from RECOVER plus additional diagnostic and quality of life measures (4.2 years post-trial on average; i.e. 50.4 months). These two observational studies were designed to facilitate longitudinal analysis of the multi-dimensional processes of recovery from OUD. See Supporting information, Figure S1, Ling *et al*. 2019 [13] and Craft *et al*. 2022 [14] for full description of the study designs and sample characteristics.

Study cohorts

We examined an analytical cohort of $n = 216$ participants who (a) completed all five initial time-points (i.e. baseline, 6, 12, 18 and 24 months) and (b) completed the baseline assessment after the inclusion of K6 as a new data point (Supporting information, Figure S2). From the initial sample, $n = 216$ participants consented to the long-term follow-up assessment (4.2 years; Supporting information, Figure S2) and were included in the long-term follow-up cohort. One hundred and fourteen participants completed all six time-points (i.e. the intersection of the analytical cohort and the long-term follow-up cohort). We used the analytical cohort to estimate the dimensions and subgroups of recovery. We used the long-term follow-up cohort to validate our subgroups.

Measures

Participant-level study measures included demographics, psychosocial variables, substance use/misuse and substance use treatment utilization. Demographic variables included age, sex, race, ethnicity, education, student status, employment and marital status at the baseline assessment. Psychosocial measures included the Beck Depression Inventory-II (BDI-II [15]), K6 [16], Short Form Health Survey (a 12-item measure of health-related quality of life; SF-12 [17]), Brief Pain Inventory (BPI [18]) and the Subjective Opiate Withdrawal Scale (SOWS [19]). Two items regarding family and social relationships, three items of physical and mental abuse and four interview quality questions regarding privacy, honesty, difficulty and substance use during the survey were included. In addition, two Likert-scale questions asking: 'I will probably be on some form of medication to treat opioid dependence throughout my life' and 'How confident are you that you can remain abstinent from abusing opioids?' were included. The long-term follow-up time-point collected additional measures to permit further understanding of recovery, including Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for OUD [20]. Remission from OUD was defined as indicating no DSM-5 criteria other than craving in the past 3 months. Self-report measures of opioid misuse in the time since the last assessment (2.3 years on average), in the past 30 days and in the past 7 days were collected. Similarly, treatment utilization was collected for the time since the last assessment and past 30 days. Medication for opioid use disorder (MOUD) utilization was determined as reported treatment with buprenorphine, methadone or naltrexone. Lastly, the World Health Organization Quality of Life Scale—Brief Version (WHOQoL-BREF) that evaluated the physical health, psychological, social relationship and environmental domains was collected.

Data analysis

Missing data

We observed two primary forms of missing data: (i) a participant who did not complete an entire time-point and (ii) missing item-level responses for a participant who did complete a time-point. We excluded all participants who had missing data in the former (i.e. missed an entire time-point). We included participants if we observed item-level missingness at any given time-point. Missing item-level responses were imputed using multivariate imputation blocked within each assessment using the MICE package in R [21]. Multivariate imputation at the block level was selected instead of mode imputation to maximize the available information.

Dimensions of recovery from OUD

A principal component analysis (PCA) was performed to identify dimensions of recovery that explain the observed variability in data. Here, PCA was implemented using the item responses from psychosocial measures, resulting in 76 variables (see Supporting information, Table S1 for a full list of variables included in the PCA). Demographics and socio-economic variables were not included in the PCA due to minimal observed variability. This PCA used observations from participants (n = 216) among all five time-points (1080 observations). Participants who had a missing time-point were excluded from this analysis. The number of principal components (PCs) was identified based on the elbow method [22] applied to the scree plot while also ensuring interpretability (Supporting information, Figure S3). Each PC corresponds to a dimension of recovery, and these dimensions are assumed to not change over time.

Identification of recovery subgroups

We used k-means clustering to identify subgroups of individuals in recovery from OUD. The PCA described above yields PCs for each participant at each time-point; we applied k-means clustering to these PCs. The total number of clusters was determined using the gap statistic [23], a commonly used metric for determining the number of clusters, while also ensuring interpretability. This allowed us to assign each participant in the analytical cohort to one of the k clusters at each of the five time-points. In addition, participants from the long-term follow-up cohort were assigned to one of the k clusters, based on the minimum distance between observed common factors and cluster centers.

Statistical analysis

Demographic characteristics were summarized using means (standard deviation) and frequencies (percentages), where appropriate. Demographics, psychosocial variables, substance use/misuse and substance use treatment utilization characteristics were compared among subgroups using an analysis of variance (ANOVA) for continuous and Fisher's exact test for categorical variables. We computed P-values in the Fisher's exact test using 20 000 Monte Carlo simulations. Using the cluster allocations and a first-order Markov transition model, we estimated the probability of transition of participants between clusters using maximum likelihood estimation. We used a likelihood ratio test to test if the resulting transition matrix probabilities varied through time (i.e. at least one transition matrix from baseline to 6 month, 6–12 months, 12–18 months and 18–24 months is different from the others) or were fixed through time. We set an a priori significance threshold of $P < 0.01$ due to the total number of outcomes tested. All analyses were performed in R version 4.0.2 [24]. The analysis was not pre-registered and the results should be considered exploratory.

RESULTS

Characteristics of the study cohort

Inclusion and exclusion of study participants are described in Supporting information, Figure S2. Baseline demographic characteristics are

TABLE 1 Demographic characteristics of the participants at baseline.

Characteristics	*n* = 216
Age[a]	43.40 (12.08)
Biological sex—female[b]	75 (34.7)
Race[a]	
Black	82 (38.0)
White	119 (55.1)
Other	15 (6.9)
Hispanic/Latino[b]	
Yes	12 (5.6)
No	200 (92.6)
Not sure	4 (1.9)
Marital status[b]	
Divorced	44 (20.4)
Married	52 (24.1)
Separated	10 (4.6)
Single	102 (47.2)
Widowed	8 (3.7)
Education level[b]	
Less than high school	35 (16.2)
High school or GED	143 (66.2)
College degree	36 (16.7)
Professional degree	2 (0.9)
Current student—yes	9 (4.2)
Employment[b]	
Employed full-time	70 (32.4)
Employed part-time	27 (12.5)
Not employed, looking for work	51 (23.6)
Not employed, not looking for work	68 (31.5)

GED = general education development.
[a]Mean (standard deviation).
[b]Endorsements (%).

described in Table 1. In summary, the majority of participants were male (65%), aged an average of 43 years, 55% white and 38% black. In addition, 66% reported completing high school or obtaining a general education development (GED) and 32% reported full-time employment. Of note, significant differences were observed between the included (n = 216) and excluded (n = 317) participants only in age (P < 0.001), race (P = 0.001) and employment (P = 0.007; Supporting information, Table S2). Demographics of individuals at the long-term follow-up did not differ appreciably from earlier time-points (Supporting information, Table S2).

Dimensions of the recovery process from OUD

We utilized a data-driven approach to identify dimensions of the recovery process from OUD. Through our PCA of participant data from the first five time-points, three dimensions (PCs) were identified (the percentage variability of each PC can be found in Supporting information, Figure S3; detailed information regarding the PC loadings can be found in Supporting information, Table S3 and Figure S4). These three dimensions explained 43.7% of the total variability in the data. The first domain, which we label depression, had BDI-II items as the strongest contributors. The second domain, opioid withdrawal, had SOWS items with the largest magnitude of factor loadings. The third domain, pain/physical health, included items from the BPI and SF-12 as primary contributors.

Subgroups of recovery from OUD

Combining data throughout all five initial time-points (1080 observations), participants were stratified using k-means clustering. In total, four subgroups of recovery were identified: high-functioning, pain/physical health (hereafter referred to as pain), depression and low-functioning. Among the subgroups, the high-functioning subgroup displayed the lowest rates of depression (BDI-II: 1.46, minimal depression), opioid withdrawal (SOWS: 1.03, mild withdrawal) and pain (BPI average pain: 0.75, no/mild pain), while the low-functioning subgroup exhibited the highest levels of all three dimensions (BDI-II: 27.69, moderate depression; SOWS: 22.02, moderately severe withdrawal; BPI average pain: 6.15, moderate–severe pain). The depression subgroup exhibited mild depression (BDI-II: 13.94, mild depression), opioid withdrawal (SOWS: 11.79, mild withdrawal) and pain (BPI average pain: 2.02, mild pain). The pain subgroup showed lower levels of both depression (BDI-II: 4.84, minimal depression) and opioid withdrawal (SOWS: 4.41, mild withdrawal) and higher levels of pain (BPI average pain: 5.63, moderate pain). Throughout all five time-points, significant differences among subgroups were observed for employment, with the high-functioning subgroup having higher rates of full-time employment and the low-functioning subgroup having higher rates of not employed and not looking for work (Ps < 0.009; Supporting information, Tables S4–S8). Overall, the SOWS, BDI, K6, social/family, BPI average pain, SF-12 and confidence in abstinence were significantly different among subgroups across all time-points (Ps < 0.006; Figure 1; Supporting information, Tables S9–S13). Significant differences were not observed among subgroups for interview quality at 18 months (P = 0.069) and perceived need for life-time MOUD at baseline (P = 0.124).

Using the previously established subgroups, we estimated subgroup assignments for participants at the long-term follow-up assessment (n = 216), a time-point that was not used when establishing recovery subgroups. Significant differences in employment among the groups was observed (P < 0.001), but not for all other demographics (Supporting information, Table S14). Overall, we continued to observe significant differences in SOWS, BDI, K6, the number of days of family and social conflicts, average BPI, need for life-time MOUD, interview quality and confidence in abstinence among subgroups (Figure 2; Supporting information, Table S15; Ps ≤ 0.001). To explore the external validity of these subgroups, we compared the WHOQoL-BREF

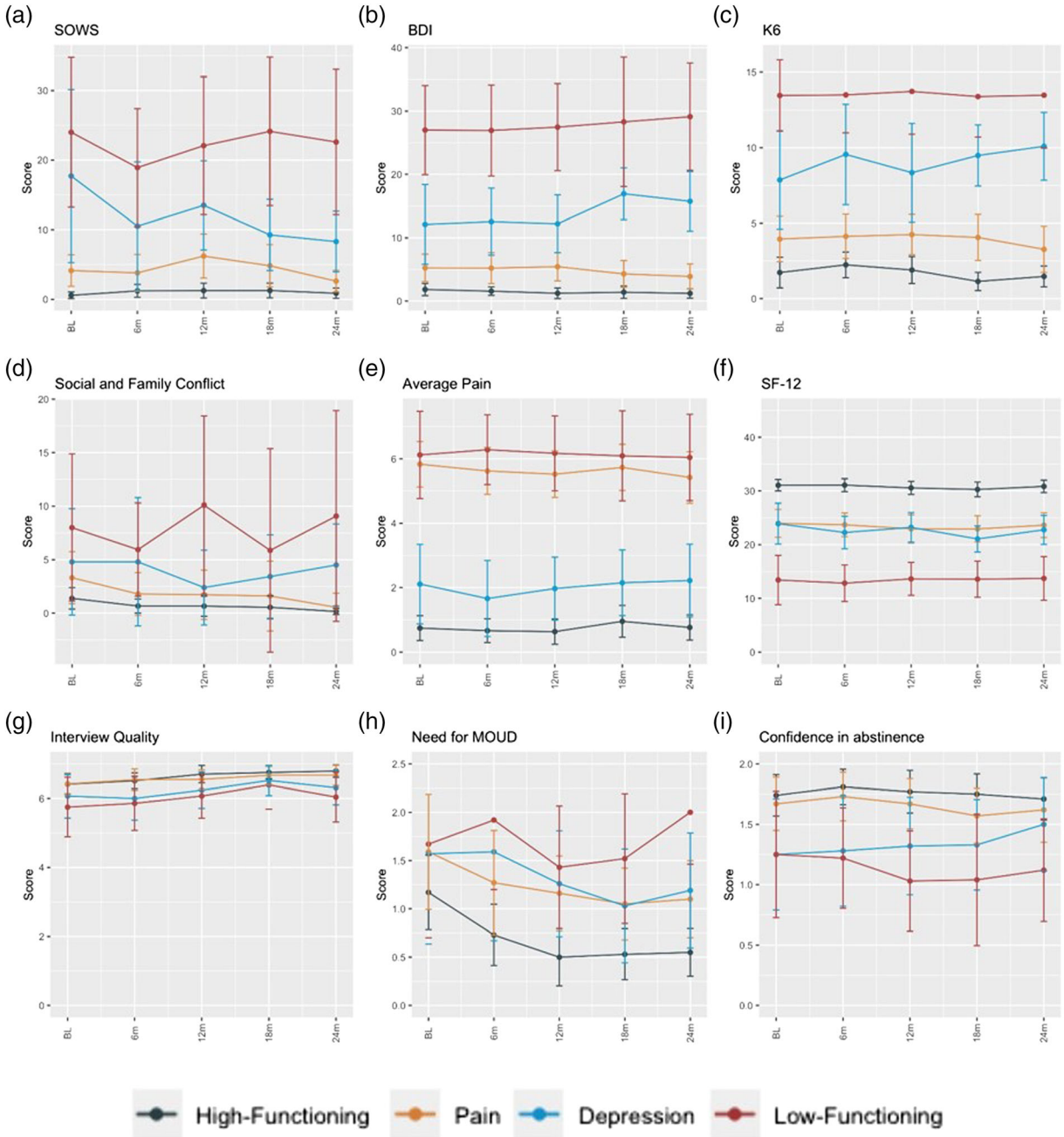

FIGURE 1 Summary of psychosocial measures by group by time-point (i.e. baseline, 6, 12, 18 and 24 months). (a) Mean SOWS scores across groups (0 = no withdrawal, 1–10 = mild withdrawal, 11–20 = moderate withdrawal, 21–30 = moderately severe withdrawal, > 30 = severe withdrawal). (b) Mean BDI-II scores across groups (0–13 = minimal depression, 14–19 = mild depression, 20–28 = moderate depression, >28 = severe depression). (c) Mean K6 scores across groups (>13 = presence of non-specific serious psychological distress). (d) Mean number of days in conflict with family and friends across groups. (e) Mean BPI average pain scores across groups (0 = absent/no pain, 1–3 = mild pain, 4–6 = moderate pain, 7–10 = severe pain[25]). (f) Mean SF-12 summed scores across groups (12 = low levels of health, 48 = high levels of health). (g) Mean interview quality scores across groups (0 = low levels of interview quality, 7 = high levels of interview quality). (h) Mean need for life-time medication for opioid use disorder (MOUD) scores across groups (0 = strongly disagree, 4 = strongly agree). (i) Mean confidence in abstinence scores across groups (0 = not at all confident, 2 = very confident). Participant subgroup assignment may change over time. BDI = Beck Depression Inventory; BPI = Brief Pain Inventory; K6 = Kessler's Psychological Distress; MOUD = medication for opioid use disorder; SF-12 = Short Form Health Survey 12; SOWS = Subjective Opiate Withdrawal Scale

scores for the four domains (physical health, psychological, social relationships and environment) across subgroups (Figure 2; Supporting information, Table S16; *P*s < 0.001, Cohen's *f* ≥ 0.62). When comparing specific subgroups, the high-functioning subgroup indicated higher quality of life for all four domains compared to the depression and low-functioning subgroups (*P*s ≤ 0.001). Significant

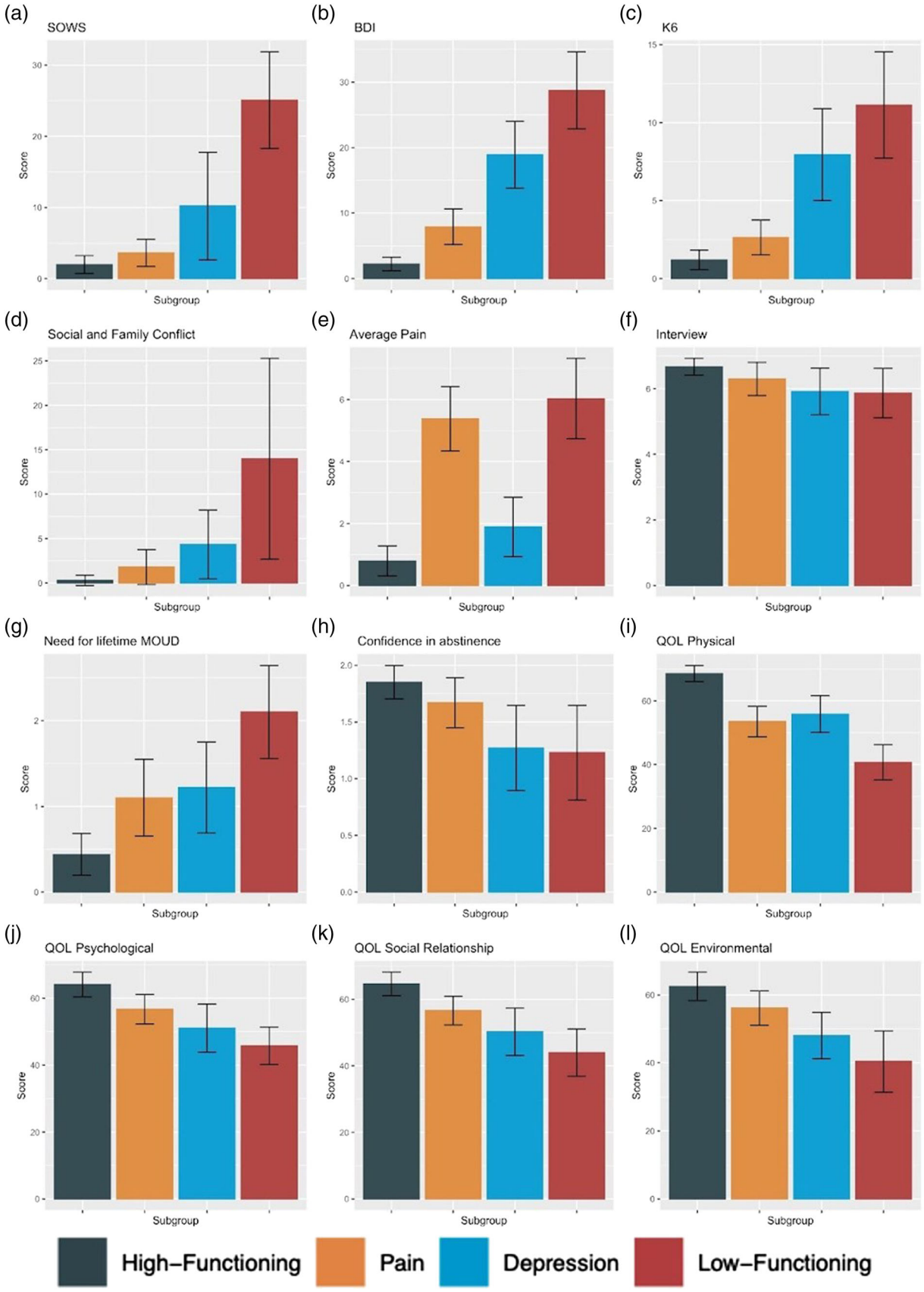

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FIGURE 2 Summary of psychosocial measures and quality of life scores across subgroups at the long-term follow-up assessment. (a) Mean SOWS scores across groups. (b) Mean BDI-II scores across subgroups. (c) Mean K6 scores across subgroups. (d) Mean number of days in conflict with family and friends across subgroups. (e) Mean BPI average pain scores across subgroups. (f) Mean interview quality scores across subgroups. (g) Mean need for life-time MOUD scores across subgroups. (h) Mean confidence in abstinence scores across subgroups. (i) Mean physical health quality of life. (j) Mean psychological quality of life. (k) Social relationships. (l) Mean environment quality of life (quality of life scores range from 0 to 100 with higher scores indicating greater quality of life). See Figure 2 caption for category thresholds. BDI = Beck Depression Inventory; K6 = Kessler's Psychological Distress; MOUD = medication for opioid use disorder; QoL = quality of life; SOWS = Subjective Opiate Withdrawal Scale

TABLE 2 Recovery, opioid misuse, alcohol use and treatment utilization outcomes across the four recovery subgroups at the long-term follow-up time-point.

n	High-functioning 87	Pain/physical health 61	Depression 37	Low-functioning 31	*P*-value
DSM-5 OUD					
DSM-5 categories (when considering the past 3 months)					< 0.001
None/mild	84 (97%)	53 (87%)	21 (57%)	7 (23%)	
Moderate/severe	3 (3%)	8 (13%)	16 (43%)	24 (77%)	
DSM-5 remission—yes	72 (83%)	41 (67%)	15 (41%)	4 (13%)	< 0.001
Opioid misuse					
Since last assessment—no	62 (71%)	37 (61%)	12 (32%)	7 (23%)	< 0.001
Past 30 days—no	74 (85%)	48 (79%)	15 (41%)	9 (29%)	< 0.001
Past 7 days—no	77 (89%)	48 (79%)	19 (51%)	11 (35%)	< 0.001
Alcohol use					
Since last assessment—no	54 (62%)	37 (61%)	16 (43%)	13 (42%)	0.091
Past 30 days—no	61 (70%)	45 (74%)	20 (54%)	17 (55%)	0.095
Past 7 days—no	72 (83%)	47 (77%)	24 (65%)	19 (61%)	0.043
Treatment utilization					
Any treatment—yes (since last assessment)	35 (40%)	38 (62%)	25 (68%)	23 (74%)	0.001
Any treatment—yes (past 30 days)	35 (40%)	38 (62%)	25 (68%)	23 (74%)	0.001
MOUD treatment—yes (since last assessment)	14 (16%)	23 (38%)	19 (51%)	19 (61%)	< 0.001
MOUD treatment—yes (past 30 days)	14 (16%)	23 (38%)	19 (51%)	19 (61%)	< 0.001

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; MOUD = medication for opioid use disorder; OUD = opioid use disorder.

differences in the physical health, psychological and environment domains were observed between the high-functioning and pain subgroups, with the latter subgroup indicating poorer quality of life (*P*s < 0.001).

Opioid misuse, substance use and treatment utilization among recovery subgroups

We investigated the prevalence of opioid use-related outcomes among the four recovery subgroups assigned at the long-term follow-up assessment ($n = 216$), including DSM-5 criteria, recent opioid misuse, recent alcohol use, recent treatment and MOUD utilization (Table 2). We identified a significant association between DSM-5 OUD severity (past 3 months) and subgroup ($P < 0.001$), with the majority of individuals in high-functioning (97%), pain (87%) and depression (57%) subgroups being in the 'none' or 'mild' OUD categories, compared to 23% of individuals in the low-functioning subgroup. Similarly, past 3-month DSM-5 remission status (i.e. meeting no DSM-5 criteria other than craving) was significantly associated with subgroups ($P < 0.001$) wherein a majority of individuals in high-functioning (83%) and pain (67%) were in remission from OUD, while fewer than half of individuals in depression (41%) and low-functioning (13%) were in remission. When examining DSM-5 criteria on a continuous scale, significant differences were observed among recovery subgroups (Supporting information, Figure S5; $F_{(3, 212)} = 51.16$; $P < 0.001$) with high- and low-functioning having the highest and lowest mean criteria, respectively. Moreover, the high-functioning and pain subgroups had significantly fewer DSM-5 symptoms than the depression and low-functioning subgroups (*P*s < 0.001).

Significant differences in opioid misuse in the time since the last assessment, past 30 days and past 7 days were observed among recovery subgroups (*P*s < 0.001) at the long-term follow-up. Specifically, the high-functioning and pain subgroups exhibited the lowest

prevalence of opioid misuse compared to the other two recovery subgroups. In contrast, significant differences in alcohol use were not observed among recovery subgroups in the three-time periods assessed (*P*s ≥ 0.043). Moreover, significant differences in treatment utilization ($P = 0.001$) and MOUD utilization ($P < 0.001$) were observed among recovery subgroups, with individuals in the low-functioning subgroup endorsing the highest rates of treatment utilization (74%). Interestingly, of those utilizing any treatment since the last assessment, more than 75% of the depression and low-functioning subgroup participants reported MOUD ($P = 0.004$).

Recovery subgroups assigned at the baseline time-point ($n = 147$) were not associated with DSM-5 OUD severity ($P = 0.65$), DSM-5 remission status ($P = 0.98$), recent opioid misuse (*P*s > 0.66), recent alcohol use (*P*s > 0.012) and any treatment utilization (*P*s > 0.04; Supporting information, Table S17) at the long-term follow-up time-point approximately 4.2 years later. A significant association was found between baseline subgroup assignment and recent utilization of MOUD ($P = 0.004$). A significant association between the subgroup at baseline and subgroup at the follow-up time-point was identified [$n = 147$; approximately 4.2 (range = 3.7–5.2) years later; $P < 0.001$], suggesting that knowledge of the current subgroup has some predictive value for longer-term future subgroup assignment but minimal predictive value for longer-term symptomology and substance use.

Transitions among OUD recovery subgroups

We tested the hypothesis that individuals remain in the same subgroup throughout their recovery. Six-month transition probabilities among subgroups in the participants were estimated (Figure 3; Supporting information, Table S18). Of note, high-functioning and pain subgroups have a 76 and 57% probability, respectively, of remaining in their subgroup 6 months later. In addition, both the high-functioning and pain subgroups have a low probability (3 and 11%, respectively) of transitioning to the low-functioning subgroup during that time. Encouragingly, participants in the low-functioning subgroup have a 48% probability of leaving the low-functioning subgroup during the next 6 months. Our findings suggest that the transition probabilities did not change throughout the study (LRT: $\chi^2_{(36)} = 37.571$; *P*-value = 0.397; Supporting information, Table S19).

DISCUSSION

This study established dimensions of long-term recovery (average = 4.2 years) from OUD and identified distinct subgroups among these individuals. We established a three-dimensional recovery perspective defined by depression, opioid withdrawal and pain/physical health. Using this three-dimensional perspective, we identified four distinct subgroups of individuals in recovery from OUD: high-functioning (minimal depression, mild withdrawal and no/mild pain), pain (minimal depression, mild withdrawal and moderate pain), depression (mild depression, mild withdrawal and mild pain) and low-functioning (moderate depression, moderate/severe withdrawal and moderate/severe pain). We found these subgroups contemporaneously aligned with diagnostic criteria (i.e. DSM-5 criteria and severity designation) and relevant OUD outcomes. Most importantly, subgroup assignments were not fixed over time and

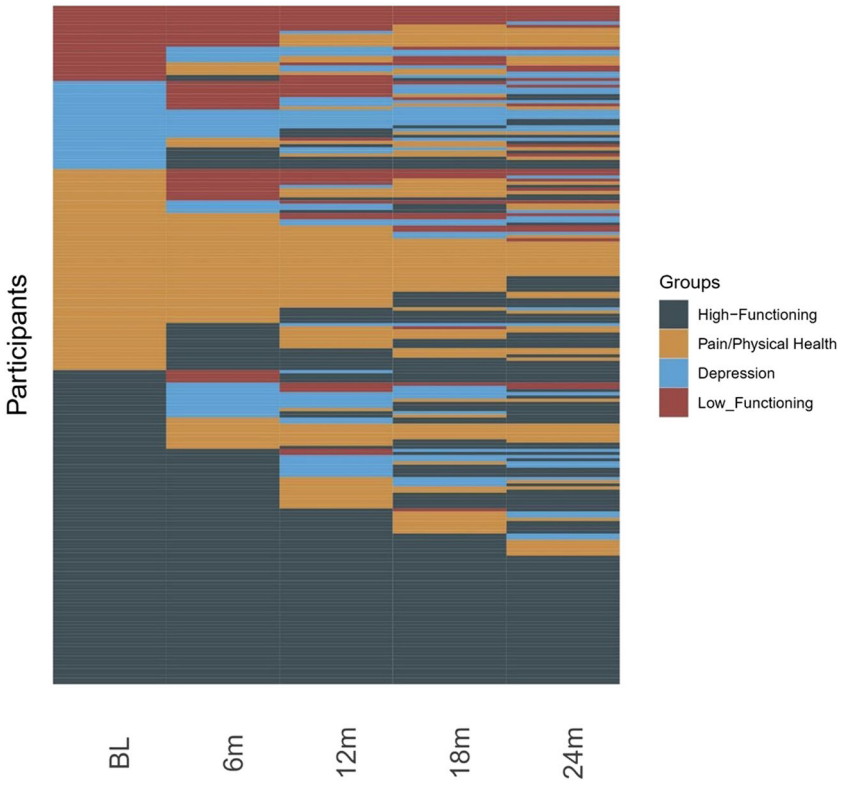

FIGURE 3 Subgroup assignment for the participants ($n = 216$). Each row corresponds to an individual participant. Each column corresponds to a time-point of data collection (i.e. baseline, 6, 12, 18 and 24 months). Changes in colors across each participant's row indicate a participant who transitions among the longitudinal study subgroups. BL = baseline; m = months

long-term recovery outcomes were not predetermined by initial subgroup assignment.

National practice guidelines for the treatment of OUD have been developed [26], but individuals in recovery require support that is proportional to their needs. Overall, our sample showed a relatively high quality of life, similar to another recovery sample [27]. However, when stratified by recovery subgroup, disparities in quality of life became apparent. Thus, our identification of distinct subgroups informs considerations for personalized OUD treatment. The relatively better psychosocial outcomes observed in the high-functioning subgroup suggest that current recovery strategies are sufficient for these individuals. In contrast, the low-functioning subgroup faces the broadest array of deficits that may require intensive treatment strategies beyond routine pharmacological (e.g. MOUD), behavioral (e.g. individual/group therapy) and/or social (e.g. mutual aid support groups) interventions. As others have also indicated, this work suggests a need to develop novel, innovative treatment strategies to support more challenging cases of OUD [28].

Pain has long been associated with OUD, as an increase in opioid prescribing to treat pain is credited with catalyzing the epidemic over the past 20 years. Individuals in the pain subgroup indicated similar quality of life scores to the high-functioning subgroup except for physical health, which is consistent with moderate pain. Unfortunately, individuals presenting with both pain and OUD are often treated for one of these ailments at the expense of the other [29]. Novel treatment strategies integrating multiple modalities including non-opioid medications and behavioral interventions may be necessary to manage these comorbid conditions [30]. Thus, identifying these individuals a priori permits targeted, holistic and innovative treatments.

OUD is highly comorbid with other mental illnesses, especially depression. This relationship is bidirectional, with opioid use associated with depression and vice versa [31]. Individuals in the depression subgroup reported the lowest quality of life. In addition to care for OUD, these individuals would probably benefit from depression-specific treatments, including pharmacological and/or behavioral interventions, to attempt to break this bidirectional relationship between opioid use and depression. By identifying individuals in each of these subgroups early, clinicians can proactively prescribe and endorse the most appropriate treatment.

The dynamic nature of the subgroup assignments demonstrates the need for continued support and assessment consistent with treating a chronic disease, and more work is necessary to identify precipitants of subgroup transitions. For instance, the high-functioning group is continuing well relative to other groups, suggesting that the treatment and/or recovery strategies are effective. Nonetheless, these individuals remain at risk for declining outcomes, with a 26% probability of transition to other subgroups at any 6-month time-point. Similarly, with the exception of higher pain, the pain subgroup is continuing relatively well with respect to the domains evaluated herein, and at any time-point have a 23% probability of transitioning to high-functioning and approximately 10% probability of transitioning to depression or low-functioning groups. In contrast, the depression and low-functioning groups had a > 50% probability of transitioning to another subgroup at any time-point, an optimistic outlook for the depression and low-functioning subgroups. Future investigation of transition precipitants has the potential to inform more holistic and integrated treatment approaches. Reinforcing the dynamic nature of subgroups and their implications for treatment is our finding that initial subgroup assignment was not predictive of key future outcomes, including DSM-5 status, opioid use and substance use treatment utilization. This lack of predetermination indicates both a hopeful and a cautionary tale. Individuals struggling after initial treatment are not doomed to suffer, while those who initially respond well to treatment should remain protective of their success.

In the context of clinical practice, these results bolster the importance of psychosocial wellbeing for individuals in recovery from OUD. The 2020 update to the ASAM National Practice Guidelines for OUD treatment state that the absence of psychosocial treatment: 'should not preclude or delay pharmacological treatment of opioid use disorder …' [26]. This guideline is important practically, given the effectiveness of MOUD and potentially limited resources of patients and/or treatment providers. However, the findings of our study emphasize the need for initial and ongoing psychosocial assessment to keep up to date with patients' needs as they move along a recovery continuum.

LIMITATIONS

This study has some limitations. First, the sample comprised individuals who participated in a clinical trial of long-acting buprenorphine, and whether or not the results discussed here are generalizable to the larger population of individuals with OUD is unknown. Secondly, our sample may be biased because we only included individuals who completed all five time-points during the first 24 months of the study, although our analyses indicated minimal differences between the included and excluded cohorts, and participant attrition resulted primarily from death or inability to locate and not from refusal to participate. Thirdly, we note that PCA assumes a linear relationship among features; existing non-linear relationships may not be captured through this approach. Fourthly, our subgroup assignments do not consider misclassification due to statistical or measurement errors. Fifthly, our methodologies did not take the repeated-measure structure into consideration, as well as the longitudinal relationship of prior subgroup status with later OUD outcomes. Lastly, while we identified four subgroups, our analyses do not preclude the existence of other subgroups. Additional research in this space to identify other potential subgroups could further inform personalized treatment.

Future directions

The evidence from this study offers a future direction for investigation. While our research identified OUD subgroups and transitions among these groups, we did not investigate factors that precipitate or prevent transition between OUD subgroups. Understanding these

factors could aid clinicians in identifying which individuals are at the highest or lowest risk of declining outcomes, thereby allowing greater precision of treatment and more efficient allocation of resources. For example, high-functioning individuals had the greatest tendency to remain in this subgroup throughout the course of this study, suggesting a level of personal resilience. Investigating factors associated with resilience during substance use recovery (e.g. emotion regulation [32]) could be a promising area of inquiry.

CONCLUSIONS

Recovery from OUD is not a unitary process; rather, it is multi-dimensional. Through this lens, we have established a multi-dimensional understanding of recovery: pain/physical health, depression and opioid withdrawal, and used these dimensions to identify four subgroups of OUD recovery. Subgroup assignments were dynamic and initial grouping did not predict long-term outcomes. These findings provide further nuance in understanding recovery and can support clinicians in providing more personalized treatment to individuals with OUD.

ACKNOWLEDGEMENT

This study was funded by Indivior, Inc., North Chesterfield, VA, USA.

DECLARATION OF INTERESTS

W.H.C., H.S., A.N.T., D.R.K., L.N.A. and M.A.R.F. have no conflicts of interests to disclose. H.C., A.LeM. and A.DeV.-G. are employees of Indivior, Inc. W.K.B. is a principal of HealthSim, LLC, BEAM Diagnostics, Inc. and Red 5 Group, LLC and is a member of the scientific advisory board for Sober Grid, Inc. and Ria Health. J.S.S. has received subcontract funding through an NIH grant awarded to BEAM Diagnostics, Inc.

AUTHOR CONTRIBUTIONS

William H. Craft: Conceptualization; data curation; formal analysis; investigation; methodology; software; validation; visualization; writing-original draft; writing-review and editing. **Hwasoo Shin:** Conceptualization; data curation; formal analysis; investigation; methodology; software; validation; visualization; writing-original draft; writing-review and editing. **Allison Tegge:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; software; supervision; validation; visualization; writing-original draft; writing-review and editing. **Diana R. Keith:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; writing-original draft; writing-review and editing. **Liqa Athamneh:** Conceptualization; data curation; formal analysis; investigation; methodology; writing-original draft; writing-review and editing. **Jeffrey Stein:** Conceptualization; data curation; formal analysis; investigation; methodology; writing-original draft; writing-review and editing. **Marco A. R. Ferreira:** Data curation; formal analysis; investigation; methodology; software; validation; visualization; writing-original draft; writing-review and editing. **Howard Chilcoat:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; software; supervision; validation; writing-original draft; writing-review and editing. **Anne Le Moigne:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; validation; writing-original draft; writing-review and editing. **Angela Deveaugh-Geiss:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; validation; writing-original draft; writing-review and editing. **Warren K Bickel:** Conceptualization; funding acquisition; investigation; methodology; project administration; resources; supervision; writing-original draft; writing-review and editing.

CLINICAL TRIAL REGISTRATIONS

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Craft WH, Shin H, Tegge AN, Keith DR, Athamneh LN, Stein JS, et al. Long-term recovery from opioid use disorder: recovery subgroups, transition states and their association with substance use, treatment and quality of life. Addiction. 2023. https://doi.org/10.1111/add.16115