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DOI: https://doi.org/10.1016/j.abrep.2022.100437

Addictive Behaviors Reports 16 (2022) 100437

Contents lists available at ScienceDirect

Addictive Behaviors Reports

journal homepage: www.elsevier.com/locate/abrep

Examining differential responses to the *Take Care of Me* trial: A latent class and moderation analysis

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ARTICLE INFO

Keywords:
Alcohol use
Emotional problems
Latent class analysis
Moderation
Online treatment

ABSTRACT

Given prevalent alcohol misuse-emotional comorbidities among young adults, we developed an internet-based integrated treatment called *Take Care of Me*. Although the treatment had an impact on several secondary outcomes, effects were not observed for the primary outcome. Therefore, the goal of the current study was to examine heterogeneity in treatment responses. The initial RCT randomized participants to either a treatment or psychoeducational control condition. We conducted an exploratory latent class analysis to distinguish individuals based on pre-treatment risk and then used moderated regressions to examine differential treatment responses based on class membership. We found evidence for three distinct groups. Most participants fell in the "low severity" group (n = 123), followed by the "moderate severity" group (n = 57) who had a higher likelihood of endorsing a previous mental health diagnosis and treatment and higher symptom severity than the low group. The "high severity" group (n = 42) endorsed a family history of alcoholism, and the highest symptom severity and executive dysfunction. Moderated regressions revealed significant class differences in treatment responses. In the treatment condition, high severity (relative to low) participants reported higher alcohol consumption and hazardous drinking and lower quality of life at follow-up, whereas moderate severity (relative to low) individuals had lower alcohol consumption at follow-up, and lower hazardous drinking at end-of-treatment. No class differences were found for participants in the control group. Higher risk individuals in the treatment condition had poorer responses to the program. Tailoring interventions to severity may be important to examine in future research.

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https://doi.org/10.1016/j.abrep.2022.100437
Received 18 February 2022; Received in revised form 1 May 2022; Accepted 29 May 2022
Available online 3 June 2022

1. Introduction

Emotional disorders (e.g., depression and anxiety) and alcohol misuse are highly comorbid and impairing among young adults (Deeken et al., 2020). Early intervention for emotional-alcohol use comorbidities in young adulthood may prevent severe, lifelong problems (Pedrelli et al., 2016), and there have been recent calls to develop more effective, accessible, integrated treatments for this population (Schouten et al., 2021). Given the need for integrated interventions, we adapted and translated the *Take Care of You* program, a successful integrated treatment for alcohol misuse and depression in German (Baumgartner et al., 2021) for use in English with content added for symptoms of anxiety. We then conducted a randomized controlled trial (RCT) to evaluate the efficacy of the intervention for alcohol misuse and emotional problems relative to a psychoeducational control. Surprisingly, we did not observe significant reductions during the intervention on our primary outcome, total weekly alcohol use. Participants in the treatment condition did, however, show larger post-treatment reductions in depressive symptoms, hazardous drinking, as well as increases in psychological quality of life and readiness for change at the end of treatment compared to the control condition (Frohlich et al., 2021). Effects on hazardous drinking and psychological quality of life were maintained at the 24-week follow-up. It is important to note that we were inclusive in our recruitment, in that we included all individuals with moderate-to-severe comorbid problems. While the program yielded some positive effects, we were left with unanswered questions, and it was important to clarify whether differential responses to treatment existed.Fig. 1a.Fig. 1b..

There is a need to examine variability in treatment responses (e.g., who treatment works or does not work for and under what conditions it works best) based on individual characteristics (Kraemer et al., 2016). Traditionally, researchers have explored this using moderation analyses, which often involves testing (one at a time) how characteristics influence treatment response (e.g., Castro, Haug, Kowatsch, Filler, & Schaub, 2017). In contrast, as argued by Lanza and Rhoades (2013), latent class analysis (LCA) is a better way to examine treatment response heterogeneity because it considers the interaction of multiple characteristics simultaneously. This allows for the identification of meaningful treatment responder subgroups. Given the complex etiology and presentation of comorbid alcohol use and emotional problems, LCA provides a comprehensive way of examining varying levels of risk within clinical samples (Müller et al., 2020).

1.1. *Predictors of substance use treatment response*

At present, specific pre-treatment factors for online integrated treatments remain unknown.

However, looking at the broader literature on moderation within brief, outpatient, substance use and mental health treatments orients us to groups of factors that are likely to be relevant for our novel integrated treatment. Most studies examining predictors of treatment response have included pre-treatment background factors such as sociodemographic information, previous treatment, prior mental health diagnoses, and family history (Amati, Banks, Greenfield, & Green, 2018; Haug & Schaub, 2016). The results remain inconclusive for whether a previous mental health diagnosis predicts positive treatment outcomes, however previous successful treatment has been shown to be beneficial for recovery among people with comorbid anxiety and depression (Amati et al., 2018). A family history of alcohol problems tends to be associated with greater symptom severity and low treatment engagement among people with alcohol use disorders (Schuler et al., 2015). The impact of gender on addiction treatment response remains inconclusive (Amati et al., 2018).

Several studies have examined the moderating impact of baseline symptom severity on responses to substance use and mental health treatment (Reins et al., 2021; Witkiewitz et al., 2017) on various clinical outcomes. A recent systematic review by Amati and colleagues (2018) examined factors that impacted recovery among individuals receiving in person psychological therapy for common mental health disorders (e.g., depression and anxiety disorders). They found that greater severity of mental health symptoms at baseline negatively impacted treatment outcomes. Similar findings have been observed for alcohol misuse interventions, where baseline emotional severity (e.g., depression, anxiety, low life satisfaction; Haug & Schaub, 2016; Witkiewitz et al., 2017), alcohol use (Cochran et al., 2016; Witkiewitz et al., 2017), and cannabis use (Bahorik et al., 2018) predicted poorer treatment outcomes (e.g., retention, problem drinking).

In addition to participant background and symptom severity, it is also important to consider pre-treatment cognitive factors that may impact individuals' engagement with treatment content. The link between poorer executive functioning (EF) skills and alcohol use is well-established (Stacy & Wiers, 2010), and EF difficulties are also common among individuals struggling with depression and anxiety (Castaneda et al., 2008). This is particularly relevant in treatments like cognitive behavioural therapy (CBT) and motivational interviewing (MI). While engaging in these treatments, clients are required to formulate goals, monitor their mood and behaviour, and complete consistent homework - all tasks that require strong EF skills. Thus, people with low EF skills may find CBT/MI particularly challenging. Indeed, Hunt and colleagues (2009) found that people with comorbid problem drinking and depression who were higher in EF had better CBT treatment responses. It follows that EF may differentially predict treatment outcomes and engagement among people with alcohol-emotional comorbidities (Domínguez-Salas et al., 2016).

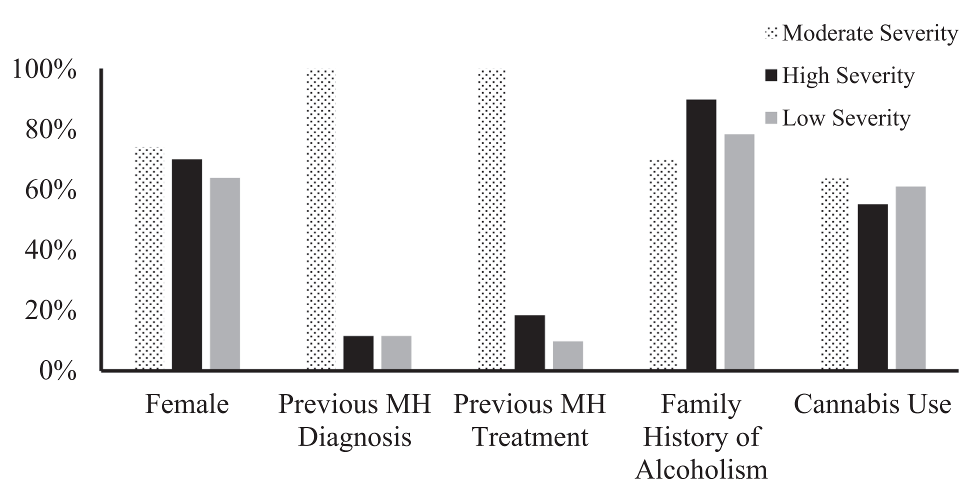

Fig. 1a. *Class Differences on* Binary *Indicators Note.* Percentages indicate the proportion of individuals in each group that endorsed the variable. MH = Mental Health.

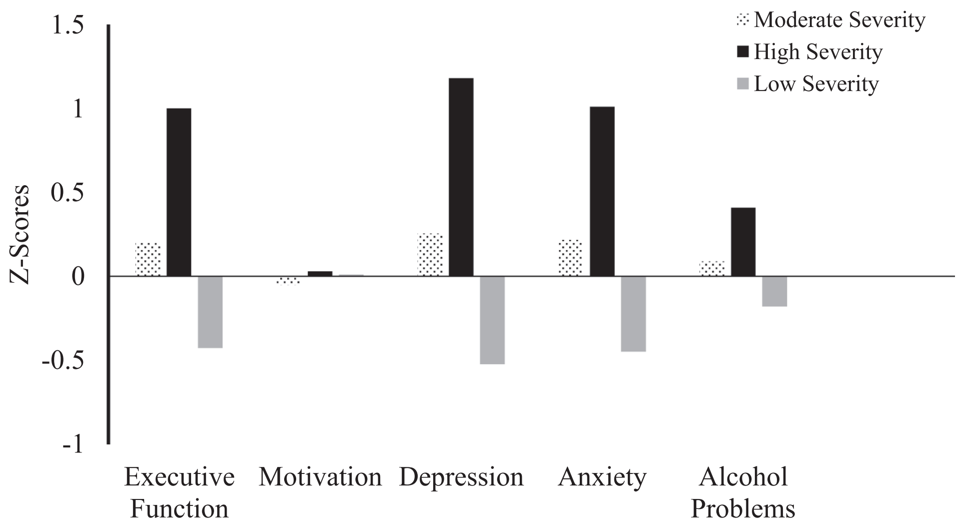

Fig. 1b. Standardized Class Differences on Continuous Indicators.

Participant motivation has also been identified as an important predictor of success in substance use treatment (Martínez-González et al., 2020). For example, Cook and colleagues (2015) found post-treatment motivation to change (i.e., being in action) had a strong association with abstinence and non-problem drinking at a 9-month follow-up. An additional study found that attitudinal barriers and readiness for change were barriers to treatment uptake (Schuler et al., 2015). It follows that motivational barriers may have adversely impacted treatment efficacy for some participants in our *Take Care of Me* program for comorbid alcohol and emotional problems.

1.2. Aims and objectives

The overarching goal of the current study was to conduct a secondary analysis of the data from the published *Take Care of Me* RCT (Frohlich et al., 2021) in order to understand heterogeneity in treatment responses. We used LCA to examine subgroups based on pre-treatment characteristics known to impact treatment response, namely *background factors* (i.e., gender, previous mental health diagnosis and treatment, family history of alcohol use), *symptom severity* (i.e., depression, anxiety, alcohol-related problems, cannabis use), *cognitive capacity* (i.e., EF), and *motivation*. It is unknown, however, what profiles of characteristics are most optimal for responding to a novel, integrated, online treatment, thus this analysis was exploratory in nature. We then used moderated regressions to explore differential program responses by subgroup for overall alcohol use, hazardous drinking, coping motives for drinking, and quality of life. The two drinking outcomes were included given the overarching goal of the intervention. Coping motives was selected as an additional outcome, given that it is a malleable cognitive factor that has been shown to be linked with severe alcohol problems (Stewart et al., 2016). Quality of life was selected as the fourth outcome because it has been shown to be an important indicator of success in mental health treatments (Kirouac et al., 2017). Overall, we expected to identify subgroups that showed differential responses to our treatment in terms of the four outcomes.

2. Method

2.1. Design

The main *Take Care of Me* study was a two-arm RCT where participants were randomly assigned to one of two conditions: the treatment condition ($n = 114$), or a psychoeducational control condition ($n = 108$). Participants in the treatment condition were provided access to 12 self-directed modules of CBT and MI to help with alcohol misuse and emotional difficulties (e.g., coping with cravings, and challenging negative thinking). Data was collected at baseline, at the end of treatment (i.e., 8 weeks), and at follow-up (i.e., 24 weeks). Participants received a $10 CAD Amazon gift card for each time point completed, for a total compensation of $30 CAD. Ethics approval was granted from the first author's institution and followed the previously published protocol (Frohlich et al., 2018). The trial was registered on clinicaltrials.gov (ID: NCT03406039). Participants ($N = 222$, $M_{age} = 24.6$, $SD_{age} = 4.37$, 67.6% female, 59.5% White) included all individuals who took part in the program. All participants reported at least moderate alcohol and emotional problems (see Frohlich et al., 2018 for detailed description of the study procedure, including full eligibility criteria). Participants were recruited using online ads, mass emails to university students, and posters in the community (e.g., addiction services, doctors' offices). Primary trial results have been recently published (Frohlich et al., 2021).

2.2. Measures

2.2.1. Latent Class Indicators.

Gender. Participants indicated (at baseline) whether they identify as a man, woman, transgender, non-binary, or other. Only one participant did not identify as either a man or woman, thus gender was coded as missing for this participant.

Psychiatric History. Participants were asked to report (at baseline) whether they had ever been diagnosed with a mental disorder, and if they had received psychological treatment in the past. If they answered "yes," which was coded as 1, they were asked to specify the diagnosis and form of treatment. Responses of "no" were coded as 0.

Family History of Alcoholism. Participants were also asked to report (at baseline) whether they believed their parent(s), sibling(s), grandparent(s), aunt(s), uncle(s), or biological cousins were problem drinkers. A binary variable was used (1 = any family history; 0 = no family history).

Cannabis Use. Participants' pre-treatment cannabis use was assessed using the cannabis item from the National Institute on Drug Abuse Alcohol, Smoking, and Substance Involvement Screening Test (National Institute on Drug Abuse, 2009). Participants indicated how often in the past three months they used cannabis on a scale ranging from 0 *(Never)* to 4 *(Daily or Almost Daily)*. Given low endorsement of use, we created a binary use variable (1 = any use; 0 = no use).

Executive Functioning. Pre-treatment EF was assessed at baseline using the 6-item WebExec (Buchanan et al., 2010). Responses ranged from 1 *(No Problems Experienced)* to 4 *(A Great Many Problems Experienced)*. Higher scores mean greater subjective problems with EF. Good internal consistency was observed in our sample (α = 0.86).

Motivation. Participants reported their levels of *readiness* and *confidence*, as well as the *importance* to make changes to improve their emotional and alcohol use issues. Responses ranged from 0 *(Not Important/Confident/Ready)* to 10 *(Very Important/Confident/Ready)*. Consistent with previous work, mean scores were created across the three items as a proxy variable for level of motivation at the outset of treatment (McNeish & Wolf, 2020).

Depression. Pre-treatment depression was assessed using the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977). Sum scores were calculated and the internal consistency at baseline was good in our sample (α = 0.86).

Anxiety. The Generalized Anxiety Disorder Scale (GAD-7; Spitzer et al., 2006) was used to assess pre-treatment anxiety. Sum scores were used, and the internal consistency was good at baseline in our sample (α = 0.80).

Alcohol Problems. Pre-treatment alcohol problems were assessed using the Alcohol Use Disorder Identification Test (AUDIT; Saunders et al., 1993), a 10-item self-report screener for past-year alcohol problems. The internal consistency at baseline was good in our sample (α = 0.86).

2.2.2. Treatment Outcomes.

Weekly Alcohol Use. Alcohol use was assessed using the Timeline Follow-Back (TLFB; Sobell & Sobell, 1992) at all three timepoints. Participants reported the number of standard drinks consumed each day for the past week (prior to each assessment survey), and a sum score was then created (reflecting total weekly alcohol use). The TLFB is widely used and is considered a reliable and valid representation of alcohol use (Pedersen et al., 2012).

Hazardous Drinking. Hazardous drinking was captured using the sum of the first three items of the AUDIT (i.e., AUDIT-C) at all three timepoints. The AUDIT-C is a widely used measure of hazardous drinking within the addictions literature (Verhoog et al., 2020).

Coping Motives. Coping motives for drinking were measured using the three-item coping subscale from the Drinking Motives Questionnaire Revised – Short Form (Kuntsche & Kuntsche, 2009) at all three timepoints. Participants respond to questions based on how often they use alcohol for coping reasons (1 *[Never]* to 3 *[Almost Always]*). The internal consistency for this sample was good (α = 0.81-0.84) across time points.

Quality of Life. Participants' quality of life was measured using the widely validated 26-item World Health Organization Quality of Life Assessment (WHOQOL Group, 1998) at all three timepoints. An overall sum score was created used and the internal consistency for this sample was good (α = 0.87-0.93) across time points.

2.3. Data analysis plan

Data were analyzed in Mplus (Muthén & Muthén, 2012). Primary results are reported in the main trial publication (Frohlich et al., 2021). The 8-week retention rate was 55% ($n = 122$), with an equal number of participants in each condition. Attrition at 24-weeks was high, with only 75 out of 222 participants remaining. In the primary trial, we speculated that high attrition may have been due to the self-guided nature of the program, which may have subsequently resulted in lower engagement and accountability with the program content and follow-up assessments. Missing data was handled using full information maximum likelihood. Regarding the main analyses, we first used LCA (Jung & Wickrama, 2007) to determine unobserved subgroups of individuals based on our selected pre-treatment factors. A total of one-through-six latent class models were tested. The fit of each class was compared against a set of indices to determine the number of distinct groups that best fit the data, namely the Bayesian information criterion (BIC; Schwartz, 1978), entropy, and the parametric bootstrapped Lo (2001) likelihood ratio test (LRT; Jung & Wickrama, 2007). Lower BIC values are indicative of a better-fitting model (Raftery, 1995). Entropy is a classification statistic ranging from 0 to 1, with values closer to 1 suggesting a more accurate classification of participants within the model. The LRT examined whether adding an additional class resulted in a significantly better model fit, whereby non-significant values suggest that the model with one fewer class should be retained. Finally, it is recommended that class sizes comprised of<5% of the total sample should not be retained. In addition to examining the fit statistics to determine model fit, it was also important to consider the theoretical interpretability within the data (Yang, 2006), such that the patterns observed among each class are clinically meaningful based on previous research.

Next, moderated regressions were used to explore the intervention by class interactions predicting immediate and longer-term follow-up outcomes. Dummy coded variables were used to represent the class variable and were used to create interaction terms with treatment condition. Class mean differences on all outcomes were examined first by conditioning models on the treatment condition, followed by reconditioning on the control condition. Baseline levels of each outcome were included in the regression models as a covariate.

3. Results

3.1. Descriptive statistics and preliminary analyses

Participants in the treatment group completed an average of 5.72 ($SD = 5.00$) modules, and only 28% completed all 12 modules. We used independent t-tests (continuous variables) and chi-square tests of independence (dichotomous variables) to examine whether individuals who completed vs. did not complete assessments differed on baseline characteristics. ☐We observed significant differences between individuals with missing vs. complete data on the TLFB ($t(220) = 2.10$, $p = .037$), full AUDIT ($t(218) = 2.94$, $p = .004$), AUDIT-C ($t(218) = 2.69$, $p = .008$), EF ($t(217) = 2.16$, $p = .032$), and family history of alcoholism $\chi^2(1, N = 222) = 9.95$, $p = .002$).

3.2. Determining the number of latent classes

See Table 1 for the fit statistics for models with one-through-six classes. LRT values were significant for each class solution, suggesting that it was important to examine the remaining fit indices. BIC values decreased from one-to-five class solutions. Class three had the highest entropy value and classification probabilities for each class exceeded 0.93, suggesting that it had the best classification accuracy. The model with four classes had subpar entropy, and models with five and six classes had some very small class sizes (<5% of the total sample). To aid in our decision making, we also considered the interpretability of the data by plotting the four-class solution. Inspection of the plots revealed minimal and less clinically meaningful differences between the three- and four-class solutions, including two groups with small sample sizes and considerable overlap on many variables. Alternatively, the three-class solution supported three distinct groups with clinically

Table 1
Fit Indices for One to Six Latent Class Growth Models.

Number of Classes	Fit Statistics			Smallest Group (%)
	SSBIC	Entropy	LRT	
1-Class	7959.544	n/a	n/a	100%
2-Class	7827.195	0.775	<0.001	34%
3-Class	**7759.011**	**0.842**	**<0.001**	**18.91%**
4-Class	7742.947	0.773	<0.001	5%
5-Class	7729.312	0.816	<0.001	3%
6-Class	7718.877	0.802	0.013	2.20%

Note. BIC = Sample-Size Adjusted Bayesian Information Criterion; LRT = Likelihood Ratio Test. Bold print indicates the retained class model.

Table 2
Class Characteristics and Statistical Tests of Group Differences from LCA.

	Class			
	1 *Moderate* ($n = 57$)	2 *High* ($n = 42$)	3 *Low* ($n = 123$)	
Continuous Variables				
	M (SD)			ANOVA
Executive Functioning	16.84 (3.91)	20.2 (3.32)	14.07 (3.70)	$F_{(2,219)} = 46.12$, $p < .001$ $\eta^2 = 0.299$
Motivation	7.20 (1.49)	7.33 (1.52)	7.30 (1.62)	$F_{(2,219)} = 0.11$, $p = .897$ $\eta^2 = 0.001$
Depression	35.56 (8.27)	44.50 (6.66)	28.02 (7.05)	$F_{(2,219)} = 83.89$, $p < .001$ $\eta^2 = 0.434$
Anxiety	13.46 (4.19)	17.02 (2.82)	10.49 (3.70)	$F_{(2,219)} = 46.12$, $p < .001$ $\eta^2 = 0.299$
Alcohol Problems	17.56 (7.43)	20.00 (9.04)	15.33 (7.50)	$F_{(2,219)} = 6.00$, $p = .003$ $\eta^2 = 0.052$
Dichotomous Variables				
	n (%)			Chi-Square
Gender				
Male	15 (26.8)	11 (26.2)	45 (36.9)	$X^2_{(2)} = 2.67$, $p = .263$,
Female	41 (73.2)	31 (73.8)	77 (63.1)	Cramer's V = 0.11
MH Diagnosis				
No	0 (0)	38 (90.5)	111 (90.2)	$X^2_{(2)} = 155.22$, $p < .001$,
Yes	56 (100)	4 (9.5)	12 (9.8)	Cramer's V = 0.84
MH Treatment				
No	0 (0)	35 (83.3)	112 (91.8)	$X^2_{(2)} = 153.59$, $p < .001$,
Yes	57 (100)	7 (16.7)	10 (8.2)	Cramer's V = 0.83
Family Hx				
No	17 (29.8)	4 (9.5)	26 (21.1)	$X^2_{(2)} = 5.97$, $p = .050$,
Yes	40 (70.2)	38 (90.5)	97 (78.9)	Cramer's V = 0.16
Cannabis Use				
No	21 (36.8)	20 (47.6)	47 (38.2)	$X^2_{(2)} = 1.41$, $p = .494$,
Yes	36 (63.2)	22 (52.4)	76 (61.8)	Cramer's V = 0.08

Note. MH = Mental Health. Family Hx = A family history of alcoholism. ANOVAs were conducted for all continuous variables, and chi-square tests were conducted for all dichotomous variables. Overall scores across groups ranged from 6 to 24 for executive functioning, 2.67–10.00 for motivation, 16–55 for depression, 1–21 for anxiety, and 3–38 for alcohol problems.

meaningful patterns on the grouping variables. Taking into consideration both fit statistics and interpretability, we had sufficient support to retain a 3-class solution to the data.

3.3. Class characteristics

Class characteristics and group differences for pre-treatment factors are in Table 2 and Figure 1. The largest group was labelled the *low severity* class (55.4% of the sample) which had the lowest endorsement of previous mental health diagnoses and treatment, and the lowest levels of baseline alcohol problems, depression, anxiety, and executive dysfunction. The second largest group was labelled the *moderate severity* class (25.7% of the sample). All people in this group endorsed a previous mental health diagnosis and mental health treatment. This group was also characterized by moderate baseline levels of alcohol problems, depression, anxiety, and executive dysfunction. The remainder of participants were classified into the *high severity* class (18.9% of the sample). These people had the highest endorsement of a family history of alcoholism, as well as the highest levels of alcohol problems, depression, anxiety, and executive dysfunction. There were no significant differences between classes for gender, cannabis use, and motivation.

3.4. Regression analyses

Separate moderated regression analyses were run for each outcome variable at both the end of treatment and at follow-up. The latent classes were summarized by two dummy codes in the models, with the low severity group as the reference class. Thus, we compared interactions between class membership and treatment condition for the high severity class versus the low severity class, and the moderate severity class versus the low severity class. Class mean differences were examined first by conditioning the model on the treatment condition, followed by reconditioning the model to get class mean differences in the control group. We expected class differences to emerge in the treatment (and not in the control) group. Given the relatively low engagement, we also conducted an exploratory analysis on whether subgroups differed on module completion. There was no significant effect of group membership on number of modules completed [$F(2,111) = 0.374$, $p = .689$].

3.4.1. Total weekly alcohol use

There were no significant class by intervention interactions at the end of treatment on the TLFB (see Table 3). However, at follow-up, the class by condition interactions were statistically significant. In the treatment group, individuals in the high severity group consumed more alcohol at follow-up than the low severity group and participants in the moderate severity group consumed less alcohol than the low severity group. We did not observe mean differences between classes when the model was reconditioned on the control group (High vs. Low Class, $B = 0.41$, $SE = 3.34$, $p = .903$; Moderate vs. Low Class, $B = -1.42$, $SE = 1.68$, $p = .339$).

3.4.2. Hazardous drinking

There was a significant class by intervention interaction for predicting hazardous drinking at the end of treatment (see Table 3). In the treatment condition, individuals in the moderate severity group had lower AUDIT-C scores at the end of treatment compared to those in the low severity group. At follow-up, a significant class by intervention interaction effect suggested that, in the treatment condition, people in the high severity group had higher AUDIT-C scores than the low severity group. In the control condition, we did not observe mean differences

Table 3
Moderated Regressions for Alcohol Use and Hazardous Drinking Outcomes at T1 and T2.

Parameter	*Estimate*	Std. Error	*B*	t	Sig.
		Outcome: Alcohol Use (TLFB)			
T1 (End of Treatment)					
Baseline TLFB	0.42	0.12	0.66	3.63	< 0.001
Intervention	−3.52	2.18	−0.16	−1.62	0.11
High vs. Low Class	−0.84	2.84	−0.03	−0.30	0.77
Moderate vs. Low Class	−2.65	2.82	−0.10	−0.94	0.35
Intervention by High vs. Low Class	−1.64	3.65	−0.04	−0.49	0.65
Intervention by Moderate vs. Low Class	1.45	3.42	0.04	0.41	0.68
R-square	0.47	0.13	–	3.61	< 0.001
T2 (Follow-up)					
Baseline TLFB	0.12	0.06	0.20	2.13	0.03
Intervention	2.64	2.95	−0.12	−0.89	0.37
High vs. Low Class	22.57	3.27	0.82	6.89	< 0.001
Moderate vs. Low Class	−8.18	2.99	−0.33	−2.74	0.01
Intervention by High vs. Low Class	**–22.16**	**4.17**	**−0.59**	**−5.32**	**< 0.001**
Intervention by Moderate vs. Low Class	**6.76**	**3.35**	**0.22**	**2.02**	**0.04**
R-square	0.59	0.07	–	8.41	< 0.001
		Outcome: Hazardous Drinking (AUDIT-C)			
T1 (End of Treatment)					
Baseline AUDIT-C	0.68	0.10	0.64	7.96	< 0.001
Intervention	−1.50	0.36	−0.32	−4.22	< 0.001
High vs. Low Class	−1.48	0.63	−0.25	−2.33	0.020
Moderate vs. Low Class	−1.27	0.47	−0.23	−2.68	0.007
Intervention by High vs. Low Class	1.63	0.99	0.20	1.65	0.100
Intervention by Moderate vs. Low Class	**1.62**	**0.72**	**0.24**	**2.26**	**0.024**
R-square	0.49	0.08	–	6.43	< 0.001
T2 (Follow-up)					
Baseline AUDIT-C	0.47	0.11	0.39	4.30	< 0.001
Intervention	−0.99	0.60	−0.19	−1.66	0.10
High vs. Low Class	3.77	0.72	0.55	5.22	< 0.001
Moderate vs. Low Class	−2.10	0.84	−0.34	−2.52	0.01
Intervention by High vs. Low Class	**−4.19**	**1.02**	−0.45	**−4.12**	**< 0.001**
Intervention by Moderate vs. Low Class	1.33	1.01	0.17	1.32	0.19
R-square	0.54	0.06	–	9.91	< 0.001

Note. For the interaction term, treatment group is the reference group. Significant interactions are bolded. TLFB = Timeline Follow-Back. AUDIT-C = Alcohol Use Disorder Identification Test – Consumption.

between classes at the end of treatment (High vs. Low Class, $B = 0.16$, $SE = 0.75$, $p = .835$; Moderate vs. Low Class, $B = 0.35$, $SE = 0.53$, $p = 0.505$) or at follow-up (High vs. Low Class, $B = -0.43$, $SE = 0.82$, $p = .606$; Moderate vs. Low Class, $B = -0.77$, $SE = 0.57$, $p = .176$).

3.4.3. Coping Motives

There were no statistically significant class by intervention interactive effects on coping motives at the end of treatment or at follow-up (see Table 4).

3.4.4. Quality of life

There were no significant class by intervention interaction effects on quality of life at the end of treatment (see Table 4). However, at follow up, a significant class by intervention interaction effect suggested that, in the treatment group, participants in the high severity group had lower quality of life scores than the low severity group. We did not observe mean differences between classes when the model was reconditioned on control group (High vs. Low Class, $B = 2.59$, $SE = 3.12$, $p = .408$; Moderate vs. Low Class, $B = 1.66$, $SE = 2.78$, $p = .550$).

4. Discussion

Given the need for accessible, integrated treatments for young adults struggling with comorbid alcohol misuse and emotional problems, we developed and examined the efficacy of the *Take Care of Me* program. We found promising evidence for 8-weeks of minimally-guided, internet-based, integrated treatment for depression, hazardous drinking, psychological quality of life, and treatment readiness (Frohlich et al., 2021). However, we did not observe significant reductions on our primary outcome of interest (i.e., total alcohol use), and were left to speculate why this may have been the case. Given our inclusive recruitment strategies (i.e., moderate or greater difficulties with alcohol use, depression, and/or anxiety), it was important to conduct secondary analyses of the trial findings to clarify potential differential responses to the treatment.

Using subtyping analyses, we were able to distinguish individuals based on shared patterns of pre-treatment characteristics, with evidence for low-, moderate-, and high-severity groups. This is one of the first studies of its kind to use LCA as a secondary analysis for an integrated treatment with the goal of capturing distinct participant profiles and heterogeneity in treatment responses (Lanza & Rhoades, 2013). While exploratory in nature, the emergence of three distinct groups is consistent with previous studies that observed varying patterns of risk for alcohol use and co-occurring emotional difficulties (e.g., Müller et al., 2020). Furthermore, participants had differential responses to treatment depending on their group membership. Individuals in the high severity group had higher levels of alcohol consumption and hazardous drinking, and lower quality of life at follow-up relative to the low severity group. This is consistent with previous research that found pre-treatment family history of alcohol problems, baseline symptom severity, and EF deficits predicted poorer responses to alcohol use treatment (Haug & Schaub, 2016; Schuler, Puttaiah, Mojtabai, & Crum, 2015; Domínguez-Salas et al., 2016). Interestingly, participants in the moderate group had significantly lower alcohol consumption at follow-up, and lower hazardous drinking at end-of-treatment relative to the low severity group, suggesting that they responded best to the program. It is possible that individuals in the high severity group struggled to engage with the minimally guided treatment as it was not matched to their needs, and they may have experienced greater difficulty applying content to their lives and making changes independently. On the other hand, those in the moderate group may have had more to gain than the low-risk group regarding symptom reduction, while also being more engaged with the

Table 4
Moderated Regressions for Coping Motives and Quality of Life Outcomes at T1 and T2.

Parameter	*Estimate*	Std. Error	*B*	t	Sig.
		Outcome: Coping Motives for Drinking			
T1 (End of Treatment)					
Baseline DMQR-SF (Cope)	0.61	0.07	0.62	8.45	< 0.001
Intervention	−0.35	0.18	−0.17	−1.20	0.05
High vs. Low Class	0.31	0.31	0.11	0.98	0.33
Moderate vs. Low Class	0.03	0.22	0.01	0.12	0.91
Intervention by High vs. Low Class	0.14	0.40	0.04	0.36	0.72
Intervention by Moderate vs. Low Class	0.55	0.32	0.19	1.74	0.08
R-square	0.49	0.06	–	7.89	< 0.001
T2 (Follow-up)					
Age	0.00	0.03	−0.01	−0.07	0.94
Baseline DMQR-SF (Cope)	0.43	0.10	0.43	4.31	< 0.001
Intervention	−0.07	0.21	−0.04	−0.24	0.81
High vs. Low Class	−0.37	0.28	−0.14	−1.30	0.20
Moderate vs. Low Class	0.18	0.44	0.07	0.30	0.69
Intervention by High vs. Low Class	1.10	0.61	0.30	1.80	0.07
Intervention by Moderate vs. Low Class	0.27	0.53	0.10	0.50	0.62
R-square	0.25	0.08	–	2.97	0.003
		Outcome: Quality of Life			
T1 (End of Treatment)					
Baseline QOL	0.80	0.09	0.63	8.97	< 0.001
Intervention	1.65	1.95	0.08	0.84	0.40
High vs. Low Class	−3.49	2.57	−0.13	−1.36	0.17
Moderate vs. Low Class	−0.99	2.33	−0.04	−0.43	0.67
Intervention by High vs. Low Class	1.88	3.75	0.05	0.50	0.62
Intervention by Moderate vs. Low Class	2.05	3.61	0.07	0.57	0.57
R-square	0.46	0.08	–	6.07	< 0.001
T2 (Follow-up)					
Baseline QOL	0.59	0.14	0.46	4.33	< 0.001
Intervention	2.17	2.52	0.10	0.86	0.30
High vs. Low Class	−12.57	2.15	−0.45	−5.85	< 0.001
Moderate vs. Low Class	4.43	6.49	0.18	0.68	0.49
Intervention by High vs. Low Class	**15.15**	**3.90**	0.39	**3.88**	**< 0.001**
Intervention by Moderate vs. Low Class	−2.77	6.96	−0.10	−0.40	0.69
R-square	0.44	0.09	–	4.86	< 0.001

Note. For the interaction term, treatment group is the reference group. Significant interactions are bolded. DMQR-SF (Cope) = Drinking Motives Questionnaire Revised – Short Form, coping subscale. QOL = World Health Organization Quality of Life Assessment.

treatment for this reason. Indeed, research suggests that individuals with some levels of risk are well-suited for brief treatment, whereas lower risk individuals may simply require a briefer intervention (e.g., a phone session; Del Boca et al., 2017).

Given the novelty and integrated nature of the *Take Care of Me* program, we were inclusive in our recruitment efforts, and were hopeful that higher-severity individuals would benefit from the program. Unfortunately, this was not the case. However, the results are consistent with previous research that found that higher baseline symptom severity resulted in greater perceived barriers to treatment and poorer clinical outcomes for alcohol misuse treatment (Haug & Schaub, 2016; Schuler, Puttaiah, Mojtabai, & Crum, 2015). Again, we were speculating that similar moderators would be relevant for online and self-guided treatments based on literature from relevant addiction treatment (e.g., outpatient CBT and MI), which appears to be the case. This is important from a clinical standpoint, as young adults with moderate symptomology may be an optimal group to target for early intervention using efforts such as minimally guided, internet-based treatment, whereas those with higher severity may require additional or more intensive treatment.

This secondary analysis shares limitations with the main manuscript, such as substantial and biased attrition at follow-up, and relatively low engagement, which were discussed in detail previously (see Frohlich et al., 2021). As such, results of both the primary trial and those in the current manuscript should be considered preliminary in nature. First, while we were sufficiently powered to run the desired analyses, our sample size was still relatively small, and this may have prevented us from finding additional meaningful subgroups. Second, due to our modest sample size, we opted to use a classify and analyze approach to examining subgroup differences on treatment outcomes rather than using the preferred three-step approach (i.e., where the LCA and regression model for class differences on distal outcomes is done within the same model). While we had very high classification accuracy (which offsets the main concern about classify and analyze approaches), future studies using the *Take Care of Me* program should recruit sufficiently larger sample sizes to use the three-step approach and, ideally, evaluate class differences on all outcomes simultaneously. Third, we only looked at short-term follow-up effects (i.e., 24-weeks), whereas helpful information about program efficacy and differential responses could be gleaned from longer-term assessments. Future versions of the program should prioritize strategies designed to improve engagement, increase sample size, and mitigate attrition. Finally, our measures of EF, family and mental health history, and cannabis use were brief and were selected to reduce participant burden. However, it is important for future work to expand on these broad measures to get a more nuanced understanding of the impact of pre-treatment factors on treatment response.

The initial results of the *Take Care of Me* trial were promising. However, given our inclusive recruitment efforts, it was important to conduct secondary analyses to gain insight into differential treatment responses. We found evidence for three distinct subgroups varying in severity based on pre-treatment factors. Individuals in the moderate severity group experienced the greatest benefits from the program relative to the high- and low-severity groups. Future programs should consider important pre-treatment factors (e.g., symptoms severity, EF) and tailor interventions accordingly to maximize treatment effectiveness.

CRediT authorship contribution statement

Jona R. Frohlich: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Karli K. Rapinda:** Resources, Writing – review & editing. **Michael P. Schaub:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **Andreas Wenger:** Software, Data curation, Writing – review & editing. **Christian Baumgartner:** Software, Writing – review & editing. **Edward A. Johnson:** Funding acquisition, Conceptualization, Writing – review & editing. **Matthijs Blankers:** Writing – review & editing. **David D. Ebert:** Writing – review & editing. **Heather D. Hadjistavropoulos:** Writing – review & editing. **Corey S. Mackenzie:** Conceptualization, Writing – review & editing. **Jeffrey D. Wardell:** Writing – review & editing. **Jason D. Edgerton:** Conceptualization, Writing – review & editing. **Matthew T. Keough:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The study was funded by a New Investigator Operating Grant from Research Manitoba awarded to M. Keough..

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