Machine Learning Analysis of Aggregated Cocaine Treatment Studies to Understand the Efficacy of Modafinil

Tan Zhu,[1] Daniel Ruskin[1], Kyle M. Kampman[2], Jinbo Bi[1]

Author Affiliations:
1. University of Connecticut, School of Engineering, Department of Computer Science and Engineering
2. University of Pennsylvania, Perelman School of medicine, University of Pennsylvania

Corresponding Author: Jinbo Bi[1]

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* jinbo.bi@uconn.edu

ABSTRACT

Aims (1) To classify cocaine dependent subjects aggregated from three studies according to cocaine use and related behavioral trajectories; and (2) to find the effect of alcohol use and other potential factors influencing the treatment of modafinil for cocaine dependence; **Design** Machine learning analysis was applied to the aggregated data from three 8-week, double blind, placebo controlled trials of modafinil for the treatment of cocaine dependence. **Setting** University of Pennsylvania Treatment Research Center (TRC). **Participants** A total of 570 cocaine dependent subjects from three independent treatment trials were included, and 366 of them were used in the trajectory analysis. **Measurements** the Brief Substance Craving Scale (BSCS), the Cocaine Selective Severity Assessments (CSSA), the Addiction Severity Index (ASI), and the results from Urine Benzoylecgonine Tests (UBT). **Findings** According to baseline screening data and repeated measurements during treatment, three subgroups were identified: subjects (29.8%) with moderate alcohol use and persistently high level of cocaine craving and withdraw symptom, subjects (33.9%) with light alcohol use, a substantial reduction of cocaine craving and withdraw symptom from a high baseline level, and subjects (36.3%) with consistently low alcohol and cocaine use, and slight reduction of cocaine craving and withdraw symptom during treatment. In the third subgroup, modafinil (200 mg/day, 300mg/day and 400 mg/day) had a significantly higher cocaine abstinence rate compared to placebo (P=0.0499). In addition, high dose modafinil (300 mg/day or 400 mg/day) had a significantly better effect than placebo on lowering the weekly cocaine abstinence rate (CI= [-0.0304,0.254], P=0.0127). **Conclusions** Modafinil has a better effect on subjects with low baseline level of cocaine craving, withdraw symptom and light alcohol use.

INTRODUCTION

Cocaine is a strong stimulant that can cause abuse and dependence. The National Survey on Drug Use and Health for 2018 reported that an estimated 5.5 million people aged 12 or older used cocaine in the past year and about 977,000 users developed cocaine dependence (CD) and abuse [1]. CD is defined as a cluster of cognitive, behavioral, and physiological symptoms that indicate continued use of cocaine, in spite of significant problems related to or caused by its consumption [2]. Cocaine use causes long-term changes in the brain [3], and is considered one of the most addictive drugs [4]. So far, the U.S. Food Drug Administration (FDA) has not yet approved any medication to treat CD [5].

Although there are no FDA-approved medications for the treatment of CD or cocaine abuse, researchers have investigated the efficacy of medications like disulfiram [6], N-acetylcysteine [7], naltrexone [8], and modafinil [2]. Though FDA approved for treating the excessive sleepiness associated with obstructive sleep apnea (OSA), shift work disorder (SWD), and narcolepsy[9], modafinil was also found to block the euphoric effects of cocaine in an early trial [10]. A later clinical trial [11] showed 23% cocaine abstinence in the modafinil group versus 9% abstinence in the placebo group (P=0.05). Until now, the mechanism of action of modafinil for the treatment of CD has not been clear; however, it has been hypothesized that modafinil may block the dopamine transporter, decrease GABA stimulation, increase hypocretin–orexin-mediated histaminergic activity ,or increase glutamate activity[2].

Although some studies have indicated that modafinil is effective in treating CD, others have failed to find any effectiveness. For example, although Kampman and

colleagues [11] showed the efficacy of modafinil by comparing the abstinence rate between a modafinil group and a placebo group, a generalized estimating equation (GEE) model did not find a significant difference under conservative assumptions (i.e. missing weeks or visits were imputed as non-abstinent). Likewise, Dackis and colleagues [12,13], found that the abstinence rate of subjects receiving modafinil was not significantly different from the abstinence rate of those receiving the placebo.

The heterogeneous clinical manifestations of CD [14,15] mean that a specific medication may not be efficacious for all cocaine-dependent individuals [2]. It is possible that modafinil is more effective for a specific subgroup of cocaine-dependent subjects than for other subgroups. For example, Dackis and colleagues found a significant interaction between male patients and the dosage of 400 mg/day of modafinil with respect to the cocaine abstinence rate[12]. Meanwhile, other studies have found modafinil effective for treating CD with no comorbid alcohol dependence [11,16–18].

In order to determine modafinil's efficacy in treating CD, it is crucial that we explore the factors causing the different findings, e.g., whether the exclusion criteria were the main factors. To achieve this goal, our study will examine the aggregated data from these prior clinical trials and use the data to identify more homogeneous subgroups that may distinguish the differential efficacy of modafinil. In the aggregated data, several measures were recorded at multiple time points (i.e., longitudinal variables), which would allow us to examine longitudinal trends in these measures. A method following the parallel latent growth mixture (PLGM) model [19], was proposed and used in this study to group subjects based on their temporal trajectories of multiple variables.

Instead of clustering subjects on the basis of a few primary outcomes [20,21], in our analysis, multiple longitudinal variables were analyzed for each individual to span the baseline and treatment periods. We used a new PLGM model that alternated in estimating the latent clusters of subjects and the trajectory parameters in iterations. The primary advantage of this new model is its ability to perform a scalable trajectory analysis with a large number of longitudinal variables. The scalability is achieved because the new trajectory analysis can be decomposed into separate analyses with each individual longitudinal variable when latent clusters are estimated and fixed**.**

MATERIALS AND METHODS

Subjects

Our study focuses on cocaine-dependent subjects who participated in three completed clinical trials at the University of Pennsylvania Medical [11–13]. In each of these three trials, subjects were diagnosed with CD based on the criteria established in the *Diagnostic and Statistical Manual of Mental Disorders*: while 1994's DSM-IV was used to diagnose those who participated in [11,12], 2000's DSM-IV-TR was used to diagnose those subjects who took part in [13]. The diagnostic criteria of cocaine abuse and dependence were the same in DSM-IV and DSM-IV-TR. In the latest DSM-5, craving was added to the diagnostic criteria, and craving was assessed in these three clinical trials. Subjects with certain concomitant conditions were excluded from these trials. Specifically, in [11,12], alcohol dependent subjects were deemed ineligible for treatment and individuals dependent on cannabis were also excluded in [11]. Additional exclusion criteria are given in a supplement. At the end, 94 out of 174 in [11], 210 out of 334 in [12], and 62 subjects in [13] were qualified for treatment in the trials.

The 366 eligible cocaine dependent subjects were included in the present study. As for the assignment of modafinil, in the first trial [11], 47 subjects received a placebo while 47 received 300 mg/day of modafinil. In the second trial [12], subjects were divided into three groups: the placebo group (N=65), the 200 mg/day of modafinil group (N=70), and the 400 mg/day of modafinil group (N=75). In the third trial [13], 32 subjects out of 62 received the placebo while the remaining received 400 mg/day of modafinil.

Measures

In total, 20 measures (17 longitudinal variables and 3 covariates) were used in our analysis, particularly in the construction of longitudinal trajectories for the subjects. Specifically, responses to the following surveys were analyzed: the Clinical Global Impression (CGI) Scale assessment [22], the Brief Substance Craving Scale (BSCS) assessment [23], the Cocaine Selective Severity Assessment (CSSA) [24], and the Addiction Severity Index (ASI) assessment [25]. Table 1 summarizes all of the repeatedly measured (longitudinal) variables. The detailed description of these variables can be found in the supplement. Additionally, age, gender, and race, three critical factors in CD subtyping [15], were used as covariates in our trajectory analysis. Noting that we didn't include education/income related features into the set of covariates because these features were used in the calculation of employment score in ASI assessment and the employment score has already included in our longitudinal analysis.

The results from the participants' Urine Benzoylecgonine Tests (UBT) were also analyzed. In the UBT, urine samples were collected from subjects and the levels of benzoylecognine (BE) in the samples were recorded. Because an individual's UBT level is

considered an objective indicator of cocaine use, our analyses used it to evaluate if a subject was abstaining from cocaine, which allowed us to evaluate the treatment's efficacy.

Data processing and aggregation

We organized the longitudinal records on a weekly level. Although the screening period consisted of one week in one study[11] and two weeks in the other two studies [12,13], we labeled the baseline file record as week 0. The baseline record included one measurement of the ASI, CSSA, BSCS, CGI, and UBT assessments. The variables of global improvement of cocaine addiction in the CGI could only be measured after the treatment started, so these variables were treated as obligated missing in week 0.

We used the data that were collected from week 0 (baseline) and week 1 (the beginning of the treatment) to week 10 (the immediate stage right after the end of treatment) in our trajectory analysis to identify subgroups of subjects based on the similarity among their longitudinal trajectories. For all three trials, the ASI was administered only at the mid-point of treatment (week 4), but the CSSA, BSCS, and CGI assessments were assessed every week during the 8-week treatment period. At follow-up, all these surveys were assessed at weeks 10, 13 and 21 in [12] or at weeks 9, 13 and 25 in [11,13]. The follow-up measures provided additional information for assessing the modafinil outcomes by subgroup.

Because the ASI variables were measured less frequently, we merged the ASI records collected at week 9 [11,13] or week 10 [12] into one data point at week 9.5 to represent the stage right after the end of treatment. This process gave us complete data at three points along the timeline to estimate the trajectory of the ASI. All other longitudinal variables were associated with the same weekly time points from week 1 to week 10.

Variables at week 9 from the second clinical trial [12] were treated as missing whereas those at week 10 from the first and third trials [11, 13] were treated as missing.

In the aggregated dataset, 16.9% of the ASI records were missing. For CSSA, BSCS, and CGI variables, the missing rates were 63.3%, 36.8% and 37% respectively. All these missing values were handled by a method called the Full Information Maximum Likelihood (FIML) [26], which we describe in a supplement.

We studied the subjects in terms of their abstinence status, which was inferred from the results of their UBTs. We adopted the criteria from the first trial [11] to select eligible urine samples. Urine samples with a temperature in the range of 90° to 100°F were considered valid and used in the calculation of the UBT variable. There were 8,381 UBT records in our aggregated dataset. Fifty tests were invalidated due to sample temperature, while 2,530 tests were missing. A urine sample was considered "positive" for cocaine if it contained at least 300ng/ml of benzoylecgonine. Because each week might have multiple UBT tests, we considered a week cocaine abstinent if all of the subject's valid urine tests in that week were negative. If no valid urine test records could be used for a week, the corresponding week was labeled as positive for cocaine, which is an accepted practice in cocaine treatment research [12] because missing samples are not ignorable, given the tendency for active cocaine users to miss clinic appointments. A subject was labeled cocaine abstinent as an outcome of modafinil treatment if the abstinence status was reported in weeks 6, 7, and 8.

Statistical machine learning analysis

We first selected the features most relevant to our study's objectives from the 17 features that were repeatedly measured in the aggregated dataset. A robust version of the

Temporal Minimum Redundancy - Maximum Relevance (TMRMR) [27] feature selection approach was applied to the aggregated data to select features in such a way that the inter-correlation between the selected measures was minimized, while the correlation between the features and the abstinence labels (based on the UBT results) was maximized.

After feature selection, the longitudinal features were normalized to achieve a comparable maximal scale between different features. Then, the normalized longitudinal features were used as input for our parallel latent growth mixture (PLGM) model. Figure 1 shows the PLGM model's path diagram, and the algorithm we used to create this model is summarized in the supplemental materials.

The PLGM model identified homogeneous subgroups of the aggregated sample and calculated the posterior probability of each subject belonging to a specific subgroup based on the observed data and estimated trajectories. Each subject was assigned to the subgroup for which they had the highest probability of membership. Then, GLM Wald χ^2-tests (for continuous variables) and independent χ^2 tests (for discrete variables) were used to determine whether the baseline measures were significantly different among subgroups. GEE Wald χ^2-tests were used to test whether the subgroups differed significantly in each of the longitudinal variables. For subjects in the same subgroup, independent χ^2 tests were conducted to test whether the dosage of modafinil affected the abstinence rate.

Then we further fitted a GEE model for the binary status of weekly cocaine abstinence ranging from week 1 to week 8 using all subjects in the subgroups that showed significant χ^2 test results on dosage. In this model, linear time trends and interactions between time and binary factors contrasting modafinil with placebo were included. .

RESULTS

The feature selection method TMRMR eliminated four longitudinal trajectories: the ASI composite legal score, the number of days of alcohol use in the last month, the ASI composite family/social score, and the Global Improvement of Cocaine Dependence. Based on the remaining thirteen longitudinal variables, the PLGM model partitioned the study subjects into three subgroups. These groups were characterized as follows: Group-1 included those subjects with moderate alcohol use, a persistently high level of cocaine craving, and withdraw symptom; Group-2 included those subjects with light alcohol use, and a clear reduction of cocaine craving and withdraw symptom from a high baseline level; and Group-3 subjects were those with consistently low use of alcohol and cocaine, and a slight reduction of cocaine craving and withdraw symptoms over time.

The baseline comparison between the groups helped determine the different addiction subtypes before any treatment effect. Table 2 was compiled by comparing the three groups on all of the measures collected at the baseline Week 0. In Table 2, there was no significant difference in demographic factors. As for other baselines, six features showed significant difference between the three groups: observed global severity of cocainedependence, self-reported global severity of cocaine dependence .

Seventeen trajectories were used to study the differential responses to modafinil by subgroup, which are shown in Figure 2, including thirteen longitudinal variables used in the PLGM model and four longitudinal variables excluded by the TMRMR. As demonstrated in Figure 2, the trajectories for Group 1 that showed high baseline values tended to maintain these high values throughout the study. Except for the ASI Employment Score (P=0.16) and the Legal Score (P=0.029), subjects in Group-1 showed higher values during the entire treatment period than the other two groups on almost all of the subfigures.

Specifically, BSCS and CSSA related measures indicate that subjects in the first group had persistent craving and withdrawal symptoms. CGI-related measures show that the global severity of cocaine addiction score hovered around four (moderate problems), and the condition of these patients was only minimally improved. In Group-2, the baseline of CSSA, CGI, and BSCS was similar to that of Group-1 but gradually dropped to the level of Group-3 (CGI and BSCS) or in between Group-1 and Group-3 (CSSA). In addition, Group-2's alcohol score was much lower than Group-1's. As for Group-3, the baseline for CSSA, CGI, and BSCS measures was lower than it was for Group-1 and Group-2. The trajectories for these measures had a time-related reduction during the treatment. And, Group-3's alcohol use was at a similar level to that of Group-2.

The percentage of subjects with complete cocaine abstinence (i.e., the rate of cocaine abstinence) was analyzed and used to assess the treatment outcome by group. Specifically, the cocaine abstinence rates in the last three weeks of the treatment (weeks 6-8) were examined. Table 3 shows the abstinence rate of subjects by group and also by the dosage of modafinil. According to Table 3, taking 200 mg/day of modafinil did not have much effect on cocaine addiction because only 3 out of the 65 subjects receiving 200 mg/day of modafinil had cocaine abstinence when the treatment approached its end. However, in Group-3, the χ^2-tests show that subjects receiving 300 mg/day and 400 mg/day of modafinil showed significantly higher rates of complete abstinence than those receiving a placebo (P=0.041 for 300 mg/day and P=0.021 for 400 mg/day).

We used the follow-up measures at later weeks (weeks 13, 21 and 25) to confirm our observations regarding the differential treatment effects among the groups. Again, missing UBT results in weeks 13, 21, or 25 were marked as positive results. The subjects

with negative results for all three of their UBTs were marked as abstinent. In Group-3, the abstinence rate was still substantially higher for those subjects using 200 mg/day, 300 mg/day or 400 mg/day of modafinil (20% of 59 subjects) than it was for those using a placebo (10% of 49 subjects in placebo, P=0.15). The decreasing cocaine use with low alcohol use in Group 2 also showed a difference in the abstinence rates for those taking modafinil and those using a placebo (15% of the 73 subjects who used modafinil versus 3% of the 33 subjects who were taking a placebo, P = 0.07). For persistent cocaine users with high alcohol use, there was no clear difference between the modafinil and the placebo groups (14% of the 50 subjects who used modafinil versus 12.5% of the 40 subjects who were taking a placebo, P=0.835).

For Group-3, being given 300 mg/day and 400 mg/day of modafinil showed treatment effects. In addition to complete abstinence, weekly cocaine abstinence was also analyzed for Group-3, as shown in Figure 3. This analysis aimed to investigate the difference between the effects of taking 300 mg/day and 400 mg/day of modafinil versus the effects of taking a placebo. Specially, the effect of 200 mg/day of modafinil was removed from the GEE model described at the end of statistical analysis, and the remaining part was used to fit the trends of weekly cocaine abstinence for each subject receiving 300/mg/day, 400 mg/day, and a placebo in Group-3. The fitting result showed that the interaction between the week and taking 400 mg/day of modafinil was significant ($\beta_{Placebo}$=-0.039, 95% CI=[-0.136,0.058], P=0.433, β_{M300}=0.082, 95% CI=[-0.032,0.197], P=0.159, β_{M400}=0.117, 95% CI=[0.025,0.210], P=0.013). In order to further analyze the difference between the modafinil and the placebo groups, we also tested the significance of the differences β_{M300}-$\beta_{Placebo}$ and β_{M400}-$\beta_{Placebo}$ (β_{M300} - $\beta_{Placebo}$=0.1211, 95% CI = [-

0.0259,0.2682], P=0.1064, $\beta_{M400} - \beta_{Placebo}$=0.1560, 95% CI=[0.0339,0.2782], P=0.0123). The significance tests' results showed that, compared with a placebo, taking 400 mg/day of modafinil has a better effect on the treatment of cocaine addiction for light cocaine users with low alcohol use.

In addition, a similar significance test was conducted by considering subjects receiving 300 mg/day and 400 mg/day of modafinil as a single group. Specifically, a GEE model was applied to fit the trends of weekly cocaine abstinence for subjects receiving a placebo and those receiving 300 mg/day or 400 mg/day of modafinil in Group 3. The result showed that the interaction between the week and the dosage of 300 or 400 mg/day of modafinil was significant ($\beta_{Placebo}$ = -0.039, 95% CI = [-0.136, 0.058], P=0.433, $\beta_{M400\&M300}$ = 0.103, 95% CI = [-0.030, 0.176], P=0.005). The difference between $\beta_{M400\&M300}$ and $\beta_{Placebo}$ was significant. The weight measuring the effectiveness of taking 300 mg/day or 400 mg/day of modafinil was significantly different from that of taking a placebo ($\beta_{M400\&M300} - \beta_{Placebo}$= 0.142, 95% CI = [-0.0304,0.254], P=0.0127).

DISCUSSION AND CONCLUSION

To the best of our knowledge, no other study has aggregated data from existing cocaine treatment trials with modafinil to study its efficacy by addiction subtype. A clear finding by our approach was that modafinil is a more effective treatment modality for subjects with a consistently low use of cocaine as well as alcohol, and these subjects may show a slight reduction of cocaine cravings and withdrawal symptoms during treatment. This finding is based on the conservative assumption that all missing visits and weeks are imputed as non-abstinent visits and weeks. The abstinence rate of subjects who received 300 mg/day or 400 mg/day of modafinil was significantly different from those who received placebos (OR=3, P=0.041 for M300 and OR=3.08, P=0.021 for M400, respectively). GEE tests also show

significant effects of week-by-dosage interactions in Group-3 between the subjects who received modafinil of 400 mg/day and a placebo as well as between the merged modafinil dosage and placebo.

These findings help explain the previous mixed results on the efficacy of modafinil for treating CD. While some early studies [12,13] struggled to evaluate its efficacy with the 400 mg/day dosage, others [11] showed that 300 mg/day of modafinil was already effective for treating cocaine dependence. The current study shows that taking modafinil of >=300 mg/day was effective only for a subset of cocaine dependents who were neither severely dependent on cocaine nor alcohol. This aligns with other trials [11,16–18] that have found modafinil to be more effective for cocaine-dependent subjects without concurrent alcohol dependence. Our trajectory analysis was able to identify Group-3 from subjects in three prior trials.

However, for subjects with little to moderate alcohol use but a persistently high level of cocaine craving and withdrawal symptoms, even high dosages of modafinil failed to take effect. We found that the cocaine abstinence rate of subjects in Group-1 was comparable to that of the subjects in the placebo group and was much lower than that of those subjects in Group-3 (χ^2 (1) = 6.25, P=0.012). Besides, there was no significant difference between the effects of 300 mg/day, or 400 mg/day of modafinil, or a placebo in treating subjects in Group-1 (χ^2 (2) =1.02, P=0.599).

There are several limitations to this study. The latest research has shown that genetic factors play important roles on addiction including CD [15,28], and cocaine has long-term effects on the brain. However, these early modafinil trials did not include genotypes, and brain signals or neuroimages. It might be more accurate to use neural markers to define subtypes and evaluate differential treatment outcomes. It can be useful to know if neural patterns or markers can be detected for the groups identified in this study. Furthermore, aside than alcohol and

cocaine use, psychiatric comorbidity or the misuse of other substances might complicate treatment effects of CD as well [29]. These assessments were not included in the aggregated data, and further examinations with more complete comorbid conditions may reveal additional subtypes to differentiate treatment outcomes.

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FIGURES AND TABLES

Table 1. Longitudinal variables used in the analysis.

Assessment	Measures
CGI	
	Self-reported global severity of cocaine dependence
	Observed global severity of cocaine dependence
	Self-reported global improvement of cocaine dependence
	Observed global improvement of cocaine dependence
CSSA	
	Total score of 18 items measuring cocaine withdrawal signs and symptoms
BSCS	
	Intensity of my craving past 24 hours
	Frequency of my craving past 24 hours
	Length of time spent in craving past 24 hours
ASI	
	ASI Composite Drug Score
	ASI Composite Alcohol Score
	ASI Composite Employment Score
	ASI Composite Legal Score
	ASI Composite Family/Social Score
	ASI Composite Psychiatric Score
	ASI Composite Medical Score
	Days of alcohol use in past 30 days
	Days of cocaine use in past 30 days

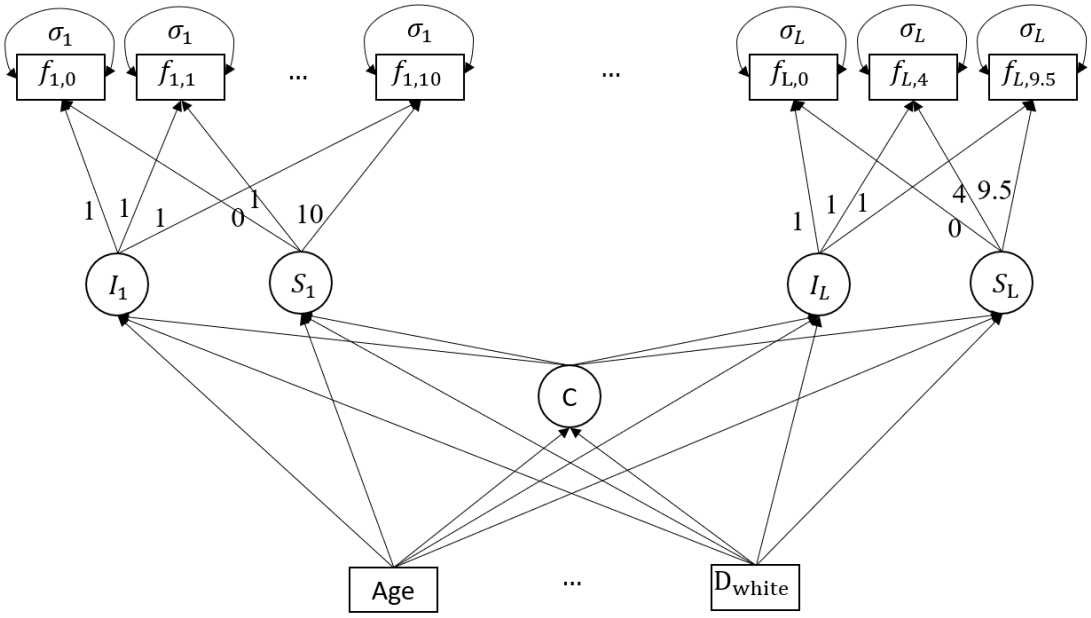


Figure 1. The parallel latent growth mixture model, where covariates are age, gender and dummy variables of race, C comprises the set of latent categorical variables measuring latent classes, I_l, S_l and σ_l are intercept, slope and variance of the l^{th} longitudinal variable. The feature values at the different time points are denoted by f_{lt}. The values belonging to ASI are $f_{l,0}, f_{l,4}, f_{l,9.5}$, while other longitudinal variables have values $f_{l,0}, f_{l,1}, \ldots, f_{l,10}$. Those numbers on the edges indicate the actual time points (for S) at which the *f* values are observed. Because the intercept does not change over time, the numbers for *I* are all ones.

Table 2: Demographic factors and baseline of the identified three clusters of subjects, expressed as percents or means (standard deviation).

Characteristics	Group1	Group2	Group3
Demographic factors			
Age	43.4504	42.7618	45.3882
Number of months in education	155.055	154.2258	151.7068
Race			
White	16	23	26
Black	87	95	100
Other	4	5	2
Gender			
Male	80	93	96
Female	29	31	37
Marital status			
Married	15	23	18
Remarried	1	2	1
Widowed	1	3	6
Separated	12	17	21
Divorced	20	28	23
Never married	60	51	64
Cocaine related feature			
Route of administration for cocaine			
Intranasal	16	25	21
Smoked	91	96	106
Injected	0	1	2
Other	2	2	4
CGI			
Observed global severity of cocainedependence*	5.8302	5.5424	5.312
Self-reported global severity of cocaine dependence*	5.7573	5.35	4.6822
BSCS			
Intensity of my craving past 24 hours*	2.4951	2.2645	1.3538
Frequency of my craving past 24 hours*	2.3495	2.2727	1.3538
Length of time spent in craving past 24 hours*	2.4854	2.157	1.3178
CSSA			
Total cocaine score*	29.0377	22.6393	15.1154
Other Cocaine Related Features			
Years of cocaine used in lifetime	13.785	13.378	12.6615
Cocaine: day spend last month*	19.6019	14.935	11.0388
Alcohol related feature			
Alcohol: day spend last month	6.9722	4.2195	3.9308
ASI composite alcohol score	0.090569	0.07232	0.056895
Other features			
ASI composite drug score*	0.27959	0.25378	0.21123
ASI composite employment score	0.64473	0.68769	0.63659
ASI composite legal score	0.06727	0.07382	0.055744
ASI composite family/social score	0.21097	0.1971	0.14032
ASI composite psychiatric score*	0.18231	0.14489	0.071566
ASI composite medical score	0.2815	0.2224	0.17617

* Significantly different ($P < .05$, Bonferroni corrected).

Table 3: Percentages of subjects who were abstinent of cocaine in the last three weeks of the treatment period (weeks 6-8).

	Group1	Group2	Group3
Placebo	2(3.8%, N=52)	4(9.5%, N=42)	5(8.3%, N=60)
M 200	1 (5%, N=20, P=0.826)	2(6.5%, N=31, P=0.637)	0(0%, N=14, P=0.598)
M 300	1 (11.1%, N=9, P=0.352)	4(28.6%, N=14, P=0.0778)	6(25.0%, N=24, P=0.0408)
M 400	1 (3.8%, N=28, P=0.951)	3(8.1%, N=37, P=0.825)	9(25.7%, N=35, P=0.0212)
M 200, 300 and 400	3(5.3%, N=57, P=0.724)	9(11.0%, N=82, P=0.803)	15(20.5%, N=73, P=0.0499)
M 300 and 400	2(5.4%, N=37, P=0.726)	7 (13.7%, N=51, P=0.532)	15(25.4%, N=59, P=0.0127)

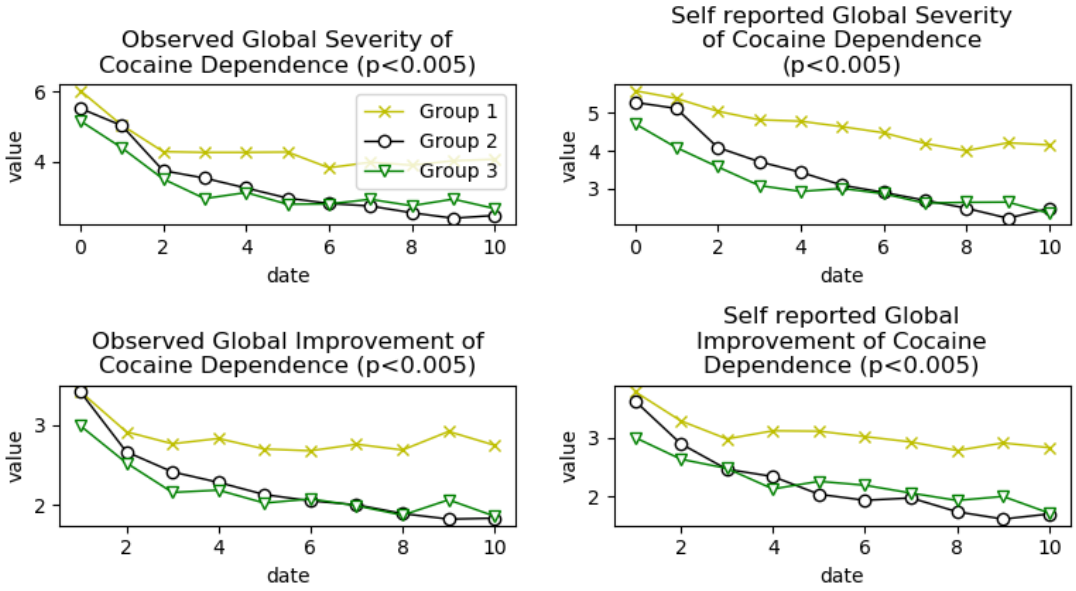
Ref: M: Modafinil, P: P-value, 200, 300 and 400: 200 mg/day, 300 mg/day and 400 mg/day;
Note: P-value were obtained via Chi-Square Test of Independence by testing whether there is significance difference between subject receiving placebo and modafinil within a group.

Table 4: Demographic factors and baseline of subjects in group3, expressed as percents or means (standard deviation).

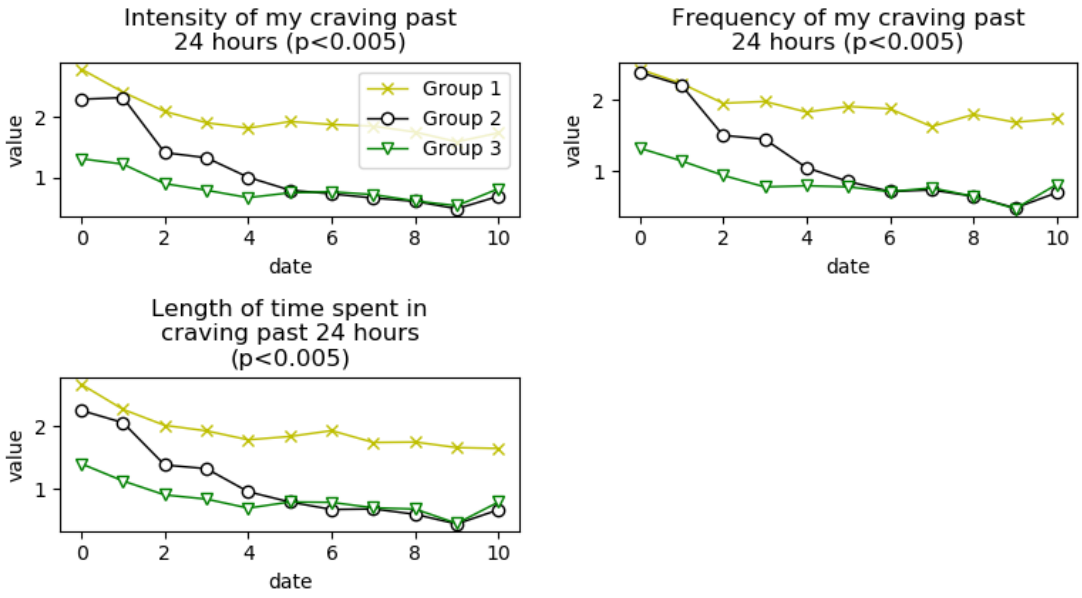
Characteristics	Placebo	300 mg/day M	400 mg/day M
Demographic factors			
Age*	44.5636	50.2013	44.3147
Number of months in education	153.5	154	149.8
Race			
White	15	3	5
Black	42	21	28
Other	0	0	0
Gender			
Male	43	21	25
Female	17	3	10
Marital status			
Married	8	2	7
Remarried	1	0	0
Widowed	3	0	3
Separated	8	6	6
Divorced	14	5	3
Never married	26	11	16
Cocaine related feature			
Route of administration for cocaine			
Intranasal	12	0	6
Smoked	43	24	28
Injected	2	0	0
Other	3	0	1
CGI			
Observed global severity of cocaine dependence*	5.3148	4.5833	5.5455
Self-reported global severity of cocaine dependence	4.8305	4.7917	4.2941
BSCS			
Intensity of my craving past 24 hours	1.3621	1.3333	1.3143
Frequency of my craving past 24 hours	1.431	1.25	1.2571
Length of time spent in craving past 24 hours	1.4211	1.1667	1.1429
CSSA			
Total cocaine score	14.8793	12.75	18.2
Other Cocaine Related Features			
Years of cocaine used in lifetime	13.785	13.378	12.6615
Cocaine: day spend last month	10.0517	10.3043	10.5588
Alcohol related feature			
Alcohol: day spend last month	3.2414	3.8333	4.3235
ASI composite alcohol score	0.052444	0.041509	0.065253
Other features			
ASI composite drug score	0.21031	0.20831	0.19937
ASI composite employment score	0.58287	0.71741	0.59584
ASI composite legal score	0.038268	0.045131	0.079552
ASI composite family/social score	0.14911	0.10491	0.1508
ASI composite psychiatric score	0.062633	0.11023	0.083636
ASI composite medical score	0.15887	0.22199	0.17824

* Significantly different ($P < .05$).

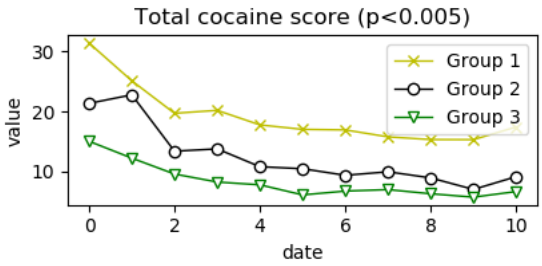
Trajectories of CGI



Trajectories of BSCS



Trajectory of CSSA



Trajectories of ASI Features

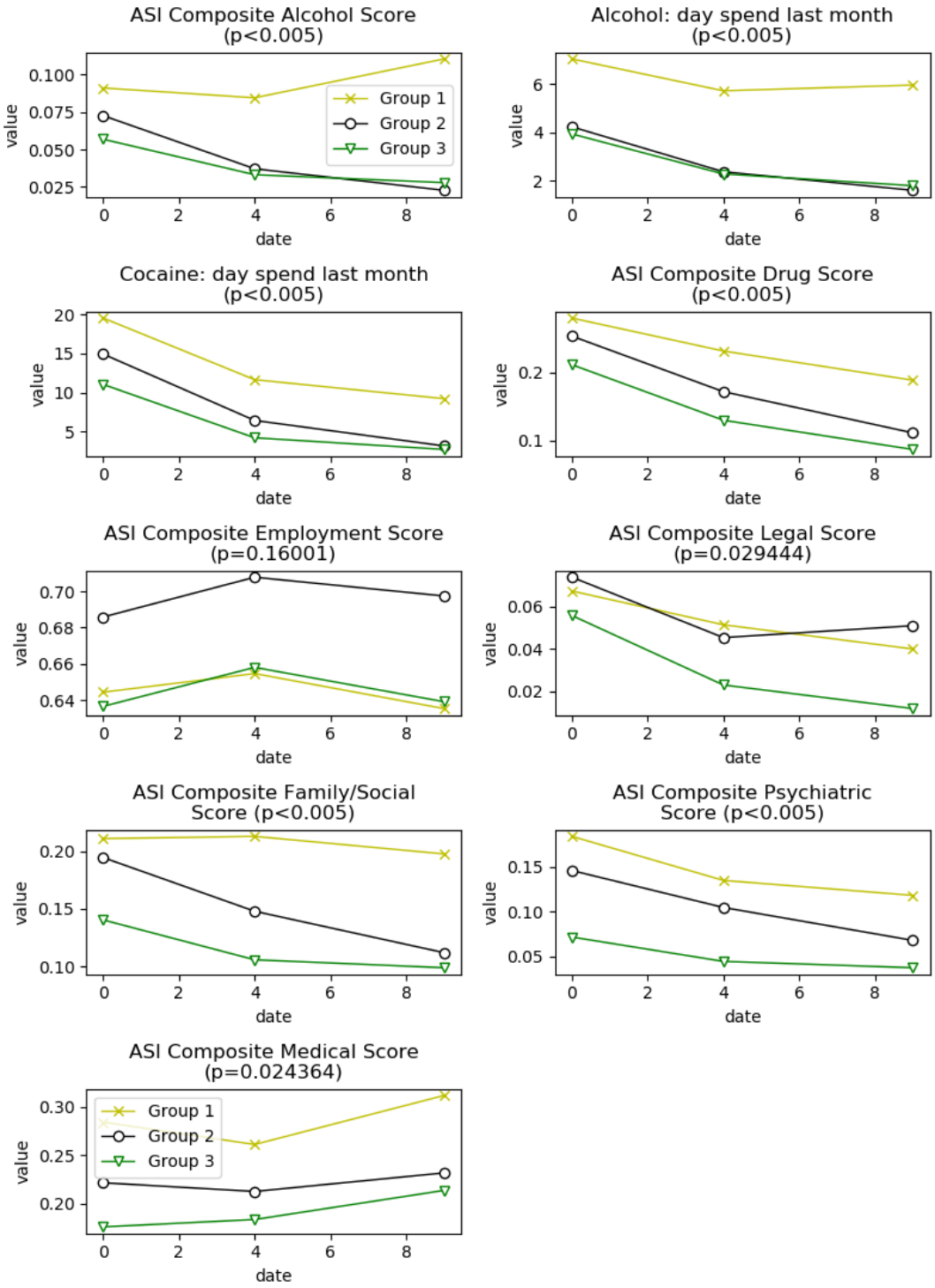


Figure 2. The characteristics of the three subgroups in the 17 longitudinal variables. The trajectory plots are organized according to the sets of measures including CGI, BSCS, CSSA, cocaine related features, alcohol related features, and ASI.

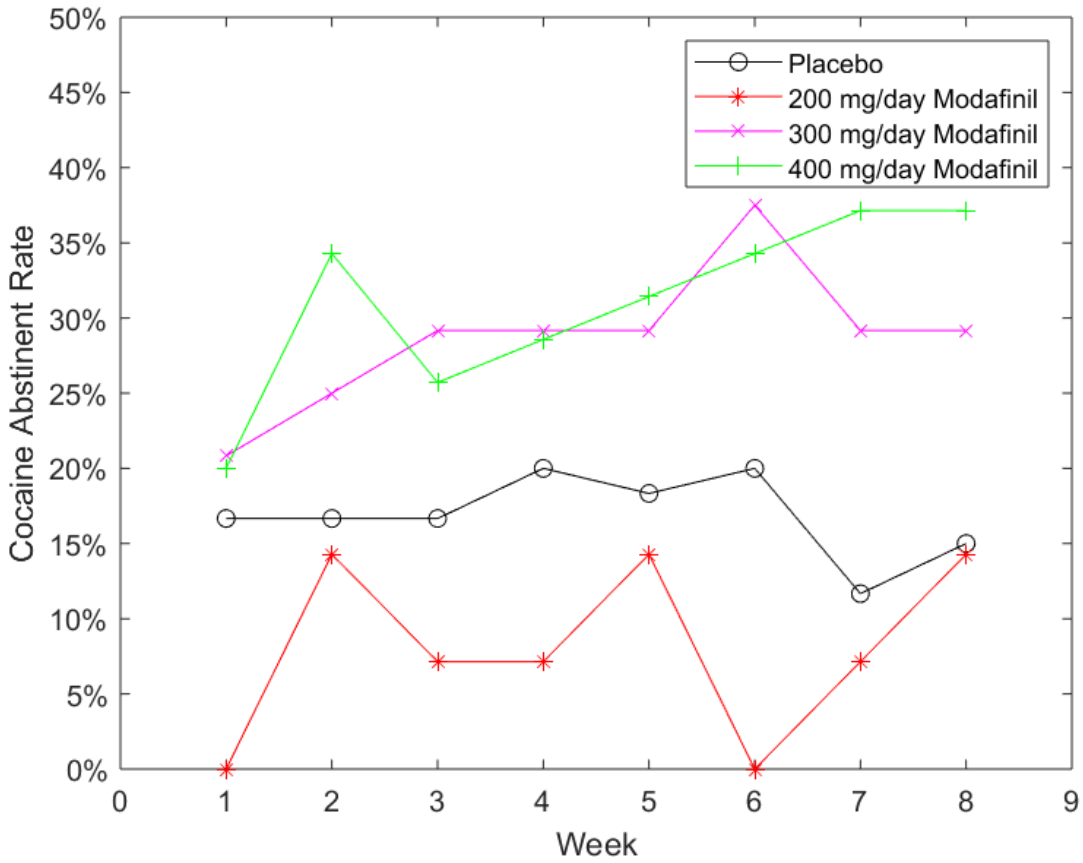


Figure 3. The trajectory of weekly cocaine abstinence rates of subjects in Group 3 by modafinil dosage.