Full length article

Acute and long-term cannabis use among stimulant users: Results from CTN-0037 Stimulant Reduction Intervention using Dosed Exercise (STRIDE) Randomized Control Trial

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A B S T R A C T

Aims: The aim of this study was to examine the impact of vigorous intensity, high dose exercise (DEI) on cannabis use among stimulant users compared to a health education intervention (HEI) using data from the Stimulant Reduction Intervention using Dosed Exercise, National Institute of Drug Abuse National Drug Treatment Clinical Trials Network Protocol Number 0037 (STRIDE).

Methods: Adults (N = 302) enrolled in the STRIDE randomized clinical trial were randomized to either the DEI or the HEI. Interventions included supervised sessions three times a week during the Acute phase (12 weeks) and once a week during the Follow-up phase (6 months). Cannabis use was measured at each assessment via Timeline Follow Back and urine drug screens. Cannabis use was compared between the groups during the Acute and Follow-up phases using both the intent-to-treat sample and a complier average causal effects (CACE) analysis.

Findings: Approximately 43% of the sample reported cannabis use at baseline. The difference in cannabis use between the DEI and HEI groups during the Acute phase was not significant. During the Follow-up phase, the days of cannabis use was significantly lower among those in the DEI group (1.20 days) compared to the HEI group (2.15 days; p = 0.04).

Conclusions: For those who adhered to the exercise intervention, vigorous intensity, high dose exercise resulted in less cannabis use. Results suggest that there were no significant short-term differences in cannabis use between the groups. Further study on the long-term impact of exercise as a treatment to reduce cannabis use should be considered.

1. Introduction

Population-based data estimates that 22 million people are current cannabis users and 4.2 million (20%) meet criteria for cannabis use disorder in the United States (Substance Abuse and Mental Health Services Administration, 2015). These estimates are extraordinarily higher than other substances, such as non-prescription use of pain relievers (4.3 million), stimulants (1.6 million), and cocaine (1.5 million), combined (Substance Abuse and Mental Health Services Administration, 2015). Furthermore, cannabis is reported to be simultaneously used with other illicit drugs, such as stimulants (Olthuis et al., 2013; Sanchez et al., 2015). Stimulants, such as cocaine, methamphetamine, and amphetamines, are often used along with other

substances, such as cannabis in treatment seeking and community-based samples (Brecht et al., 2008). For example, a multistate study (Booth et al., 2006) found significantly greater use of cannabis among methamphetamine and cocaine users.

Despite its common use and increasing prevalence of abuse and dependence (Substance Abuse and Mental Health Services Administration, 2016, 2017), there are limited approved medical treatments to reduce cannabis use. Treatment thus far has relied on generic substance use reduction behavioral approaches (Budney et al., 2007; Buchowski et al., 2011). Exercise is an example of a potential behavioral approach to reduce cannabis use. Despite study limitations, exercise has been documented to have the potential to assist with tobacco smoking cessation (Marcus et al., 2005; Ussher et al., 2008);

however, there are limited studies that explore the impact on cannabis use. A pilot study found that aerobic exercise training reduced cannabis craving and use in cannabis-dependent adults (Buchowski et al., 2011). However, the pilot study measured cannabis via self-report and the sample size was small.

Exercise as an approach to reduce cannabis use has the potential to provide physical and mental health benefits. A review of the literature (Brellenthin and Koltyn, 2016) found no randomized control trials that have examined the potential impact of exercise as a treatment option to reduce cannabis use; however, authors identified exercise as a promising treatment option due to its low cost, accessibility, and lack of negative stigma (Brellenthin and Koltyn, 2016). Exercise, even in short bouts, has been shown to improve sleep and mental health (Catalan-Matamoros et al., 2016; Meyer et al., 2016; Kelley and Kelley, 2017). Cannabis users reported using the substance to improve these outcomes; therefore, providing exercise as a treatment option may reduce cannabis use due to its positive impact on the aforementioned poor health outcomes (Brellenthin and Koltyn, 2016). A pilot study conducted on 12 non-treatment seeking adults with cannabis use disorder found aerobic exercise training reduced cannabis craving and use (Buchowski et al., 2011); however, there were limitations to the study. Cannabis use was measured via self-report with no objective measure confirmation. Furthermore, the pilot study's aerobic exercise training program included 10-sessions over the course of two weeks, with a follow-up period of an additional two weeks. The short, two-week follow-up period of the pilot study resulted in the inability to assess the long-term impact (beyond two weeks) of the aerobic exercise training program on cannabis use reduction.

Despite the positive outcomes of exercise training, there is a lack of randomized trials testing such relationships. The objective of the current study was to examine the impact of a vigorous intensity high dose exercise intervention (DEI) on cannabis use compared to a health education intervention (HEI) among stimulant users. It was hypothesized that stimulant users randomized to DEI would have significantly lower cannabis use than HEI.

2. Methods

2.1. Study overview

The current study is a secondary analysis of cannabis outcomes from the Stimulant Reduction Intervention using Dosed Exercise (STRIDE), National Institute of Drug Abuse Clinical Trials Network Protocol Number 0037. The aim of the parent study (Trivedi et al., 2011, 2017), the STRIDE clinical trial, was to examine the efficacy of an aerobic exercise intervention in reducing stimulant use. Reduction in cannabis use was not the primary outcome of interest in the parent study. Details regarding the design, protocol, and methods of the STRIDE clinical trial have been described elsewhere (Trivedi et al., 2011; Greer et al., 2012; Stoutenberg et al., 2012; Rethorst et al., 2014; Walker et al., 2014). Details of the study are described in the following sections. The protocol and materials were approved by the Institutional Review Board at each of the nine participating sites. The STRIDE clinical trial was registered at Clinicaltrials.gov (identifier: NCT01141608).

2.2. Study population

Adults (18–65 years): (1) were admitted to a residential substance abuse treatment program; (2) reported the use of stimulants within 30-days prior to enrollment; (3) met DSM-IV criteria for stimulant abuse or dependence within the past year; and (4) medically cleared to exercise via a protocol-defined stress test. At screening, adults who: (1) were opioid dependent within the past year; (2) presented with a medical or psychiatric condition that prohibited study participation; (3) tested positive for pregnancy; (4) were unable to perform aerobic exercise more than 3 days per week for 20 min; and/or (5) were currently

performing aerobic exercise more than 3 days a week were excluded from study enrollment.

2.3. Study procedures

The parent study's aim was to compare stimulant abstinence between the DEI (n = 152) and the HEI (n = 150) groups. The study was divided into an Acute phase (Weeks 1–12) and a Follow-up phase (Weeks 13–37). Details of the interventions are provided elsewhere (Trivedi et al., 2011; Greer et al., 2012; Stoutenberg et al., 2012; Rethorst et al., 2014; Walker et al., 2014). In brief, participants were randomly assigned to either DEI or HEI. Baseline assessment and randomization typically occurred within one week of residential substance abuse treatment program admission. The Acute phase of both interventions consisted of supervised sessions three times per week for 12 weeks. Participant transition out of residential substance abuse treatment program occurred during the Acute phase. The average length of residential substance abuse treatment program status was 18.1 days. The Follow-up phase of both interventions consisted of attendance at one weekly supervised session. Both groups received comparable time commitment, investigator contact, and received the interventions from trained facilitators at the residential substance abuse treatment program from which they were recruited. All participants received addiction treatment as usual.

2.3.1. Dosed exercise intervention

Participants randomized to the DEI group received an exercise dose of 12 kcal/kg/week (KKW) at an intensity of 70–85% of maximal heart rate. The dose was designed to be equivalent to 150-min of moderate exercise per week. Specifically, participants began with a 5-min active warm up on the treadmill. Polar RS 400 heart rate monitors (Kempele, Finland) were used to monitor participants' heart rate and to confirm that all participants remained in their individualized target heart rate zone (i.e., 70–85% of an individual's heart rate max). The speed and/or incline of the treadmill was continually adjusted based on maintaining the participant's target heart rate zone. At the end of the exercise session, participants completed a 5-minute active cool down period to return their heart rate to within 15% of their resting rate. Finally, participants were led through a 5- to 10-min stretching routine to end their exercise session. During the follow-up phase, trained exercise facilitators helped participants plan logistics and troubleshoot as needed with regard to finding a location to continue their exercise sessions. Participants recorded their rated perceived exertion based on a scale of 1 (lowest) to ten (highest).

2.3.2. Health education intervention

Participants randomized to the HEI group received information on health-related topics such as mental health, nutrition, and sleep distributed to participants via didactic lectures, website references, audio, video, and written materials for reference. Information on exercise training was not included in the HEI. Participants in this group had the same number of visits per week as the DEI group. The rationale for using HEI as the control group is described in detail elsewhere (Greer et al., 2012; Rethorst et al., 2014). In brief, HEI was chosen to reduce potential threats to internal validity by ensuring both groups received comparable contact with study staff. Furthermore, HEI has been found to be ineffective but equivalent in attention as a control condition in other related studies (Marcus et al., 1999; Rejeski et al., 2005; LIFE Study Investigators, L. S., et al., 2006).

2.4. Measures

2.4.1. Cannabis use

The Timeline Follow Back (TLFB) was administered at each assessment during Acute and Follow-up phases to capture self-reported cannabis and other substance use information. The TLFB is a validated

semi-structured interview that uses calendar prompts to recall daily substance use over a specific period of time (Sobell et al., 1996; Robinson et al., 2014). Participants were also administered urine drug screens three times per week during the Acute phase and weekly during the Follow-up phase of the study. The Eliminate Contradiction (ELCON) algorithm (Oden et al., 2011) was used to reconcile the TLFB with the urine drug screens. When the urine drug screen was positive, but the prior three days were negative according to the TLFB, the TLFB for the last day in the window was changed from negative to positive. Cannabis use was calculated using this algorithm during the post- residential substance abuse treatment program period from the day after discharge to 84 days after randomization. Days of cannabis use was then converted to a use per 30-day scale.

2.4.2. Non-Drug use measures

Age, sex, race/ethnicity, employment status, years of education, and marital status were collected at screening. At baseline, several self-report measures were collected. Details of their collection are described elsewhere (Trivedi et al., 2011; Greer et al., 2012; Stoutenberg et al., 2012; Rethorst et al., 2014; Trivedi et al., 2017). Briefly, the Stimulant Selective Severity Assessment (SSSA) assessed stimulant abstinence; the Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ) assessed quality of life; the Quick Inventory of Depressive Symptomatology (QIDS-C) assessed depression; the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) (Fava et al., 2006) assessed physical and cognitive functioning; and problems associated with substance use was assessed using the Addiction Severity Index-Lite (ASI-Lite) (McLellan et al., 1980). Attendance to the addiction treatment as usual was assessed using a study-specific treatment tracking form.

2.5. Statistical analysis

Cannabis use was compared between the DEI and HEI groups during the Acute and Follow-up phases using both the intent-to-treat (ITT) sample and the complier average causal effects (CACE) analysis, as applied to the primary outcome of stimulant use in the parent study (Trivedi et al., 2017; Carmody et al., 2018). In the Acute phase, cannabis use was defined via days of use based on the ELCON algorithm that combined the TLFB and urine drug screen from the day after discharge from RTP to the end of the Acute phase (day 84). For the Follow-up phase, days of use from the beginning of the Follow-up phase to the end (day 252) were counted. Cannabis use was analyzed using a Hurdle Model due to excess zeros reported. The Hurdle Model approach results in two outcomes. First, the probability of any use is calculated for the sample that used cannabis. Second, for those that reported use, the frequency of use (days of use) is calculated. The Hurdle Model included a random site effect and a fixed treatment group effect with days of use of cannabis in the 30-days prior to residential treatment entry, age, and sex as covariates. Effect sizes for the probability of use and days of use among users were derived from the coefficient estimates and standard errors of the hurdle models where the sample size used for the HEI group in the CACE analysis was the sum of the propensity score weights.

For the CACE analysis, a participant was considered adherent if exercise averaged greater than the median observed exercise dose (8.3 KKW or more per week in the Acute phase and 4.2 KKW per week or more in the Follow-up phase). The CACE adjustment requires a model to estimate propensity score weights as described elsewhere (Stuart and Jo, 2015). The predictors used in the model were selected from a comprehensive list of potential predictors based on the inclusion criteria of p < 0.20. The CACE propensity score model was created using a machine learning technique. Separate models were derived for the Acute and Follow-up phases because: 1) there were dropouts who did not complete the Follow-up phase; and 2) the median-split cutoff for adherence was lower in the Follow-up phase than the Acute phase.

Table 1
Sample demographics and clinical characteristics.

	Total N = 302	Dosed Exercise Intervention n = 152	Health Education Intervention n = 150
Demographic			
Sex			
Male	181 (60%)	89 (59%)	92 (61%)
Female	121 (40%)	63 (41%)	58 (39%)
Age, mean (SD)	39.0 (11)	38.5 (10)	39.5 (11)
Race/Ethnicity			
Black	130 (43%)	55 (36%)	75 (50%)
White	137 (45%)	74 (49%)	63 (42%)
Hispanic	31 (10%)	19 (13%)	12 (8%)
Education in years, mean (SD)	12.4 (2)	12.4 (2)	12.3 (2)
Marital status			
Married	40 (13%)	23 (15%)	17 (11%)
Divorced/Separated/Widowed	101 (33%)	55 (36%)	46 (31%)
Never married	161 (53%)	74 (49%)	87 (58%)
Employment status			
Full time	133 (44%)	63 (41%)	70 (47%)
Part time	53 (18%)	23 (15%)	30 (20%)
Unemployed	92 (30%)	55 (36%)	37 (25%)
Other	24 (8%)	11 (7%)	13 (9%)
Cannabis Use/Treatment			
Days in residential treatment, mean (SD)	18.1 (10)	18.3 (11)	17.9 (10)
Days of cannabis use in 30 days prior to treatment admission, mean (SD)	4.4 (8)	4.0 (8)	4.7 (8)
Prevalence of cannabis use in 30 days prior to treatment admission, n (%)	131 (43%)	67 (45%)	64 (42%)
Cannabis Dependence Diagnosis, n (%)	96 (32%)	49 (32%)	47 (31%)

However, the same modeling procedure was used for both the Acute and Follow-up phases. In order to achieve balance between groups, the following baseline covariates were added (in addition to prior drug use, age, and sex): ASI Drug Subscale, percent attendance at addiction treatment as usual sessions prior to randomization, the SSSA hyperphagia item, age of onset of maximum use of any drug, SSSA total score, years of education, QLESQ, CAST slept well item, and ASI satisfaction with usual living arrangement item.

3. Results

Demographic and baseline clinical characteristics are presented in Table 1. Forty-three percent (43.4%) reported cannabis use in the 30-days prior to residential treatment admission and 32% had Cannabis Dependence Diagnosis. During the Acute phase, 23.4% reported cannabis use. Of the 226 participants who did not test positive or report cannabis use at baseline, 33 initiated use during the Acute phase. Of the 271 participants who provided data for analysis in the Follow-up phase, 118 (43.5%) reported cannabis use at baseline, 79 of whom reported use during the Follow-up phase. During the Follow-up phase, 28.1% of participants who reported no cannabis use at baseline-initiated cannabis use.

3.1. Intention to treat hurdle model results

Table 2 presents the Acute and Follow-up phase TLFB results for cannabis use. The Hurdle Model generated results for the probability of use and days of use among users. The difference in cannabis use between the DEI and HEI groups during the Acute and Follow-up phases were generally small. There were no significant differences in days of cannabis use between the DEI (1.85 days/30 days) and HEI group (2.00

Table 2
Intention to treat treatment group effect on cannabis use via the hurdle model.

Phase	Dosed Exercise Intervention n = 152 Days of use/ 30 days	Health Education Intervention n = 150 Days of use/ 30 days	Coefficient[*]	Standard Error	Coefficient Effect Size	Z-Value	p-value
Acute	1.85	2.00	−0.077	0.24	0.019	−0.3	0.74
Follow-Up	2.27	2.63	−0.155	0.12	0.075	−1.3	0.20

Phase	Probability of Use	Probability of Use	Coefficient[*]	Standard Error	Coefficient Effect Size	Z-Value	p-value
Acute	0.326	0.335	−0.039	0.18	0.013	0.2	0.82
Follow-Up	0.423	0.475	−0.207	0.23	0.052	0.9	0.36

[*] Hurdle model coefficient for treatment group effect.

days/30 days; p = 0.74). In the Follow-up phase, cannabis users in the DEI group used cannabis 2.27 days/30 days compared to 2.63 days/30 days among users in the HEI group (p = 0.20).

3.2. CACE adjusted hurdle model results

Table 3 contains the model estimated days of use and probability of use among cannabis users for each group. During the Acute phase, the days of cannabis use was numerically lower in DEI (1.50 days/30 days) compared to HEI (1.91 days/30 days); however, it was not statistically significant (p = 0.47). Furthermore, the probability of use was numerically lower in the DEI group than the HEI group for cannabis use, but the difference was not statistically significant (p = 0.64). During the Follow-up phase, the days of cannabis use was significantly (p = 0.04) lower among those in the DEI group (1.20 days/30 days) compared to the HEI group (2.15 days/30 days). The probability of use was numerically lower in the DEI group (33.0) than the HEI group (43.2), but it was not statistically significant (p = 0.23).

4. Discussion

The current study sought to examine the impact of vigorous intensity high dose exercise intervention (DEI) on cannabis use among stimulant users compared to a health education intervention (HEI). It was hypothesized that cannabis use would be lower among those randomized to the DEI group compared to the HEI group. Results suggest that there were no significant short-term differences in cannabis use between the two groups. However, there were long-term differences between participants in the DEI and HEI groups. Specifically, those who adhered to the DEI had a lower frequency of cannabis use than those in the HEI group during the Follow-up phase.

A review of the literature found no randomized control trials that have examined the potential impact of exercise as a treatment option to reduce cannabis use; however, authors identified exercise as a promising treatment option due to its low cost, accessibility, and lack of

negative stigma (Brellenthin and Koltyn, 2016). A pilot study conducted on 12 non-treatment seeking adults with cannabis use disorder found aerobic exercise training reduced cannabis craving and use (Buchowski et al., 2011); however, there were limitations to the study. Cannabis use was measured via self-report with no objective measure confirmation. In order to increase accuracy of the measurement of cannabis use, our study collected self-reported cannabis use via the TLFB supplemented by urine drug screens that were collected throughout the duration of the study. Furthermore, the pilot study's aerobic exercise training program included 10-sessions over the course of two weeks, with a follow-up period of an additional two weeks. The short, two-week follow-up period of the pilot study resulted in the inability to assess the long-term impact (beyond two weeks) of the aerobic exercise training program on cannabis use reduction. In the current study, participants in the DEI group received an exercise dose in the Acute phase (Weeks 1–12) and the Follow-up phase (Weeks 13–37).

Although the frequency of cannabis use was not significantly lower among the DEI group during the Acute phase, the frequency of use was lower during the Follow-up phase among those who were adherent to the DEI. The length of the Follow-up phase provides time for the participants to get into a routine, rather than administering an intervention over a shorter period of time where a long-term behavior change may not be as likely to occur. Reduction of cannabis use found in the Follow-up phase among this population of stimulant users is important because it provides preliminary evidence for future studies to examine the sustainability of the impact of an exercise intervention well after the program has ended.

Results from the current study suggest that there was a long-term difference in cannabis use among those who adhered to the DEI during the Follow-up phase. A possible explanation for the reduction of cannabis use in this population could involve the overall improvement of physical and mental health that generally results from engaging in physical activity, noted in previous studies (Catalan-Matamoros et al., 2016; Meyer et al., 2016; Kelley and Kelley, 2017). Although STRIDE was a randomized clinical trial designed for stimulant users in

Table 3
Complier average causal effect adjusted treatment group effects.

Phase	Dosed Exercise Intervention n = 75 Days of use/ 30 days	Health Education Intervention n = 146 Days of use/ 30 days	Coefficient[*]	Standard Error	Z-Value	p-value
Acute	1.50	1.91	−0.244	0.34	−0.7	0.472
Follow-Up	1.20	2.15	−0.582	0.29	−2.0	0.044

Phase	Probability of Use	Probability of Use	Coefficient[*]	Standard Error	Z-Value	p-value
Acute	0.230	0.263	−0.174	0.38	−0.5	0.643
Follow-Up	0.330	0.432	−0.437	0.37	−1.2	0.232

[*] Hurdle model coefficient for treatment group effect.

residential treatment centers, the indirect impact on long-term reductions of cannabis use is advantageous given the high prevalence of polysubstance use among stimulant users. Further, reducing cannabis use may potentially have an impact on reducing stimulant use as previous work has shown that the odds of engaging in stimulant use increased 3-fold among cannabis users compared to non-cannabis users.

One of the strengths of the study is the randomized trial design. All participants received addiction treatment as usual and had similar time commitment in each arm of the study (DEI and HEI). Second, the current study included continuous multi-measurement of cannabis use. Participants were assessed via self-report throughout the study parallel to urine drug screens at every intervention session. The multiple measurements result in highly accurate estimate of current cannabis use. A post-hoc analysis of the ASI confirmed that the majority of cannabis users (99.5%) smoked the cannabis and only 2 participants reported using cannabis orally; therefore, route of cannabis administration was homogenous in this population. Third, the DEI group engaged in structured exercise three times a week over a prolonged period of time, a dose and intensity that has not been replicated previously. Finally, the exercise sessions began within the residential substance abuse treatment program which had the potential to lead to habit-forming behavior. Participants were in residential substance abuse treatment program for an average of 18 days of the 37-week intervention; therefore, translating this intervention to non- residential substance abuse treatment program settings is plausible given the Follow-up phase reduction of cannabis use.

Despite the strengths, the study has limitations as well. First, results can only be generalized to adults with stimulant dependence; however, the study was conducted in nine residential treatment programs across the United States, thus increasing geographical generalizability. Second, the CACE analysis has some limitations to note. The CACE analysis relies on propensity score models to estimate hypothetical adherence to exercise in participants who were randomized to the health education condition. While we employed a comprehensive approach to calculating the propensity scores, it is possible that there were unmeasured factors that predict exercise adherence in our sample. Such omission of important predictors of exercise adherence would bias the models. Interpretation of our results should account for these limitations. Third, there may be an inherent challenge to maintaining a consistent exercise program among a portion of the population. Notably, less than 5% of the general adult population in the United States engages in 30 minutes of physical activity a day (U.S. Department of Health and Human Services, 2017); thus, there may be challenges to maintain consistent engagement in exercise. Results from our study suggest that cannabis users who adhered to the exercise intervention may experience reduction in long-term cannabis use, as observed during the Follow-up phase of the study. This phase is meant to represent community/non-residential intervention settings. Future studies may consider examining strategies aimed at maintaining adherence to exercise interventions in this population.

5. Conclusion

In conclusion, among cannabis users who adhered to the exercise intervention, vigorous intensity high dose exercise was found to have an impact on reducing cannabis use during the Follow-up phase of this randomized trial of stimulant users. Results suggest that there were no significant short-term differences in the reduction of cannabis use between the DEI and HEI groups. Further studies on the impact of exercise on cannabis use among non-stimulant users are needed to assess whether exercise may be a potential treatment option to reduce its use.

Contributors

Drs. Greer and Trivedi designed the study and wrote the protocol. Dr. Carmody led the statistical analyses. Drs. Vidot and Rethorst drafted

the manuscript. Drs. Stoutenberg and Walker assisted with data interpretation and manuscript review. All authors contributed to and have approved the final manuscript.

Conflicts of interest

Dr. Carmody received an honorarium from the University of Texas San Antonio. Dr. Greer has received research funding from NARSAD and has received honoraria and consulting fees from H. Lundbeck A/S and Takeda Pharmaceuticals International, Inc. Dr. Trivedi has received funding support from the Agency for Healthcare Research and Quality (AHRQ), Cyberonics Inc., National Alliance for Research in Schizophrenia and Depression, National Institute of Mental Health (NIMH), National Institute on Drug Abuse (NIDA), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Johnson and Johnson. He has received advisor/consultant fees from Abbott Laboratories Inc., Akzo (Organon Pharmaceuticals Inc.), Allergan Sales LLC, Alkermes, Arcadia Pharmaceuticals Inc., AstraZeneca, Axon Advisors, Brintellix, Bristol-Myers Squibb Company, Cephalon Inc., Cerecor, Eli Lilly and Company, Evotec, Fabre Kramer Pharmaceuticals Inc., Forest Pharmaceuticals, GlaxoSmithKline, Global Medical Education Inc., Health Research Associates, Johnson and Johnson, Lundbeck, MedAvante, Medscape, Medtronic, Merck, Mitsubishi Tanabe Pharma Development America Inc., MSI Methylation Sciences Inc., Nestle Health Science-PamLab Inc., Naurex, Neuronetics, One Carbon Therapeutics Ltd., Otsuka Pharmaceuticals, Pamlab, Parke-Davis Pharmaceuticals Inc., Pfizer Inc., PgxHealth, Phoenix Marketing Solutions, Rexahn Pharmaceuticals, Ridge Diagnostics, Roche Products Ltd., Sepracor, SHIRE Development, Sierra, SK Life and Science, Sunovion, Takeda, Tal Medical/Puretech Venture, Targacept, Transcept, VantagePoint, Vivus, and Wyeth-Ayerst Laboratories.

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