Decreasing Cocaine Use with Repetitive Transcranial Magnetic Stimulation

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Kate Ziesenheim

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Decreasing Cocaine Use with Repetitive Transcranial Magnetic Stimulation

Abstract

Background: Dependence on cocaine causes significant functional impairment and morbidity in users and is extremely prevalent in the U.S. Unlike other abused substances, there is currently no effective standard of treatment to decrease cocaine cravings and prevent relapse. This systematic review assesses whether recent research shows that repetitive transcranial magnetic stimulation (rTMS) is an effective treatment to decrease cocaine use.

Methods: An exhaustive search of the medical literature databases was performed using Medline-Ovid, CINAHL, and Web of Science with the search words “cocaine” and “transcranial magnetic stimulation”. The studies reviewed were chosen based on inclusion and exclusion criteria and were assessed for quality using the GRADE criteria.

Results: There have only been two studies performed on rTMS's effects on cocaine use specifically, which were both included in this review. Both studies showed evidence that rTMS decreases cocaine use. One study showed a significant increase in abstinence during, and up to 6 months after rTMS treatment and a significant decrease in cravings as a secondary outcome. The second study did not show a significant decrease in cocaine use for the rTMS group until an exploratory analysis was done. The quality of both studies was low to moderate based on the GRADE criteria.

Conclusion: Despite the small number of studies assessing rTMS's effectiveness on decreasing cocaine use and their low to moderate quality of evidence based on the GRADE criteria, the 2 studies reviewed here show promising evidence that rTMS can successfully decrease cocaine use. Trials with a larger sample size and higher attrition rate are required to more clearly show whether rTMS has a positive effect on decreasing cocaine use. Despite these limitations, since effective treatments are not currently available, the risk of rTMS treatment is low, and the cost of continued cocaine dependence is extremely high, rTMS treatment should be considered for patients trying to abstain from cocaine use.

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Degree Name
Master of Science in Physician Assistant Studies

Keywords
Cocaine, Transcranial magnetic stimulation, Cocaine use disorder, dopamine, dorsolateral prefrontal cortex, nucleus accumbens

Subject Categories
Medicine and Health Sciences

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Decreasing Cocaine Use with Repetitive Transcranial Magnetic Stimulation

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A Clinical Graduate Project Submitted to the Faculty of the
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Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

[redacted]
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Keywords: Cocaine and transcranial magnetic stimulation

Acknowledgements

[redacted]
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List of Abbreviations

ACC anterior cingulate cortex  
CUD cocaine use disorder  
DA dopamine  
DA D2 dopamine D2 receptors  
DLPFC dorsolateral prefrontal cortex  
MDD major depressive disorder  
NAc nucleus accumbens  
PFC prefrontal cortex  
rTMS repetitive transcranial magnetic stimulation  
RCT randomized controlled trial  
TMS transcranial magnetic stimulation  
VTA-NAc ventral tegmental area – nucleus accumbens pathway
Decreasing Cocaine Use with Repetitive Transcranial Magnetic Stimulation

BACKGROUND

Cocaine causes morbidity of multiple organ systems, increased risk taking, violent behavior, and fetal drug exposure. There were an estimated 18.2 million cocaine users worldwide in 2016,1 which is about 0.3-0.4% of the population 15-65 years old.1 Individuals with cocaine use disorder (CUD) tend to chronically relapse after attempts to abstain, in part because there are currently no proven effective pharmacological, psychotherapy, or somatic treatments to help individuals quit using.2,3

A study3 has shown that cocaine users have decreased brain volume and neurotransmitter dysfunction. Cocaine use increases dopamine release in the reward system part of the brain, the Ventral Tegmental Area – Nucleus Accumbens Pathway (VTA-NAc), which contributes to the addictive nature of the drug. After individuals with CUD are detoxed, there is a decrease in dopamine D2 receptors (DA D2) and dopamine (DA) release in the VTA-NAc pathway4,5 which contributes to relapse as the detoxed individuals crave dopamine. Additionally, there is a decrease in dorsolateral prefrontal cortex (DLPFC) activity in individuals with CUD. The DLPFC transmits dopamine to the anterior cingulate cortex (ACC), which is involved in inhibitory control over rewarding stimulus. Decreased dopamine transmission from the DLPFC to the ACC can cause loss of control over cocaine cravings.3,4 Thus, increasing dopamine may decrease the chance of relapse.4

Repetitive transcranial magnetic stimulation (rTMS) has been used since 1985 to treat individuals with depression and has been proven to be extremely effective and relatively safe. In 2008, the U.S. FDA approved rTMS as a treatment for depression and many insurances now cover the procedure.
An enormous amount of research has also been done in the last seven years to show the effectiveness of rTMS on decreasing alcohol and nicotine cravings. The dopaminergic pathway that is responsible for cravings in cocaine are the same pathways involved in alcohol and nicotine dependence and to some extent responsible for depression. 

Repetitive transcranial magnetic stimulation (rTMS) provides a relatively safe, non-invasive, non-pharmacological treatment by electromagnetically stimulating neural pathways in the brain and changing dysfunctional neural circuits. The extent and depth of rTMS depends on the shape and size of the coil used to deliver magnetic stimulation to the brain. Traditional rTMS uses a figure-of-eight coil which stimulates the cortex about 2-2.5cm deep. The H-coil stimulates the subcortex up to 6 cm deep and is shown to have more consistent results than the figure-of-eight coil. The 5 studies that have been completed on the use of rTMS to treat CUD and reduce cocaine craving, use either the figure-of-eight or the H-coil. Theta Burst Stimulation (iTBS) is a new form of rTMS. Two studies currently in progress have been submitted to NIH that assess the effectiveness of iTBS on cocaine use and cravings.

Of the 5 studies that have been completed on the use of rTMS to treat CUD, 4 of the studies used ratings of cravings as an outcome, and 2 of the studies used cocaine use as an outcome. This review evaluates the 2 studies that used cocaine use as an outcome, since this outcome appears to be a more reliable objective measure of the effectiveness of rTMS than subjective ratings of cocaine cravings.

METHODS

An exhaustive search of medical literature databases was performed using MEDLINE-Ovid, CINAHL-EBSCO, and Web of Science with the search words “cocaine” and “transcranial magnetic stimulation”. Eligible studies for this review were published in the English language
and used human subjects only. A search of the National Institute of Health database for ongoing trials was performed to be used in the discussion of future research. The 5 studies that were found that used rTMS to treat cocaine use were reviewed. The selected studies were assessed for quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.16

RESULTS

Fifty-six articles were found during the initial search of Web of Science, 3 from MEDLINE-Ovid and 4 from CINAHL. All 3 of the results from MEDLINE and 3 of the results from CINAHL were duplicates of the results from Web of Science. All of the titles of the articles were screened to find studies that met the inclusion criteria. The abstracts of 20 studies that appeared to meet inclusion criteria from the nature of the titles were read. Five studies that used rTMS to treat cocaine dependence were read in full. These studies used either cocaine cravings or cocaine use as an outcome. Trials using cocaine use as an outcome were chosen as the subject of this review due to being a more objective measure of decreasing cocaine use than cocaine cravings and decreasing cocaine use as being the ultimate goal of cocaine treatment. There were 2 RCTs3,4 that met all inclusion criteria for this review of literature. See Table 1. Six articles were found that reviewed rTMS’s effects on substance abuse in general and one specifically on rTMS’s effects on cocaine. These articles were read for background information on the subject. The National Institute for Health’s website was searched to find any ongoing trials. There is currently one trial in process that meets criteria for this review that is not recruiting yet.
Bolloni et al

The Bolloni et al study, conducted at the National Health Institute of Addiction of Marsciano, Italy in November of 2014, was a double blinded randomized controlled trial (RCT) in which subjects were either assigned to a rTMS treatment group or a sham group that received a placebo treatment of rTMS. The experimental procedure of the trial compared the 2 groups for cocaine use by analyzing the subject’s hair samples at time T0 (before treatment), T1 (end of treatment 4 weeks later), T2 (3 months post treatment), and T3 (6 months post treatment). The hair samples were tested for quantities of cocaine, cannabis, and opioids using a set of guidelines provided by the Society of Hair Testing. Originally there were a total of 18 subjects identified with CUD seeking outpatient treatment. Inclusion criteria were patients aged 18 and 65 years, with a minimum cocaine use of 0.05-20 ng/mg at least 2 days per week for the 4 weeks leading up to the trial, and with the ability to comprehend and sign the informed consent form. Exclusion criteria were patients with other substance use disorders, ongoing mental health issues, serious medical illness, requiring the use of medical devices, history of epilepsy, pregnancy, or current enrollment in other clinical trials. Of the 18 patients identified, 4 subjects were dismissed from the trial for cocaine use levels higher than the accepted range. Four other subjects did not finish the treatment phase and were labeled as dropouts. By the end of the study, 10 subjects (8 males, 2 females) were included in the statistical analysis. See Table 2.

The treatment group received 10 hz stimulations from a H1-coil rTMS device aimed to stimulate the prefrontal cortex bilaterally. There were 12 stimulations, 3 per week, spaced equally over the 4-week treatment period. Each stimulation consisted of 20 runs of 50 pulses with 15 second breaks between, totaling 1000 pulses in a 10-minute session. The same treatment setting and schedule was used with the sham group using an rTMS device that made an identical
sound as functioning machines without emitting magnetic stimulation. Initially there was no major outcome difference regarding cocaine use between the 2 groups; however, an exploratory analysis using a one-way analysis of variance was conducted to assess the use of cocaine over time. The exploratory analysis showed a significant decrease in cocaine use from time T0-T2 and T0-T3 in the treatment group, but not the sham group.4

Limitations of this study were its small sample size and participant attrition. The initial subject pool of 18 people was quickly reduced to 14 when initial cocaine amounts were detected. There were 4 patients that dropped out during treatment for unknown reasons, reducing the final sample size to 10 people. The authors of the study acknowledged these limitations and advocate for a larger trial to help strengthen the findings of future trials.4

Terraneo et al

The Terraneo et al study was conducted in Italy by the Department of Outpatient Neuroscience at the University of Padua. It was a between subject, open label, RCT where eligible individuals were randomly assigned to a treatment group who received rTMS to the dorsal-lateral prefrontal cortex (DLPFC) or a control group who were administered an established protocol pharmacological treatment for CUD. Subjects were assessed for cocaine use during the study by urine analysis to quantify the outcome of the interventions. The study was divided into 3 stages: Stage 0 (recruitment), Stage 1 (29-day treatment), and Stage 2 (an additional 63-day follow-up). Secondary outcomes such as cocaine craving (see Figure 1) and depression were monitored during this study; however, because of the subjectivity of these outcomes and the Bollini et al study not measuring these outcomes, these results will not be discussed in depth.
Inclusion criteria for this study were patients between 18 and 70 years old, with a diagnosis of CUD, and actively seeking outpatient treatment for CUD. The study excluded subjects who were currently pregnant or had a diagnosis of major depressive disorder, bipolar disorder, schizophrenia, other psychotic disorders, or another substance use disorder. Medical exclusion criteria were subjects who had a history of epilepsy or seizures, or had electronic medical devices. Stage 0 yielded 32 qualifying participants who were randomized into standard (pharmacological) and experimental (rTMS) treatments. See Table 3.

The pharmacologic intervention was established by the Department of Neuroscience at the University of Padua and consisted of pramipexole 0.35 mg TID, oxazepam 15 mg TID, bupropion 150 mg daily, triazolam 0.25 mg daily, and gamma hydroxybutyrate 1.75 g daily. This combination of medications reduces cravings for substances as well as reducing anxiety, depression, and sleep symptoms that often accompany cocaine discontinuance. The experimental group received rTMS from a MagPro R30 stimulator device that was meticulously calibrated to target the subject’s left DLPFC. MRI was initially used to locate the desired point of stimulation, and the coordinates were marked on a cap with which the subject had been fitted. The cap was then used for the duration of treatment. The stimulation doses were delivered in 60 pulse trains at 15 hz frequency. Forty simulation trains with 15 second rests were administered each session totaling 2400 total pulses per 13-minute treatment. Abstinence of alcohol use was a requirement for both groups and a daily dose of disulfiram, a medication which is an emetic if alcohol is ingested, was given to all participants to deter alcohol consumption.

The treatment period, Stage 1, was 29 days for both the experimental and the standard groups. The experimental group was given 1 rTMS treatment per day for the first 5 days, then
once a week for the following 3 weeks, totaling 8 rTMS treatments. The standard group received pharmacologic treatment for the entire treatment stage.

The follow-up period, Stage 2, lasted 63 days. During this time, the standard group was given the choice of continuing pharmacologic treatment or switching to rTMS treatment and tapering off the medication. Ten of the standard participants chose to switch to rTMS (n=10), 1 discontinued the study, and 2 continued pharmacologic treatment. Both the standard and experimental group had one participant who discontinued treatment during the follow up period, resulting in a 6% loss of participants over the course of the trial.

The study reported a positive outcome if a subject did not test positive for cocaine on any of the urinalysis tests during the experimental phase and a negative outcome if there were any positive tests. The treatment group had 69% positive outcomes and the standard group had 19%, showing that there was a statistically significant positive outcome in the treatment group (p=0.035). The authors used a logistic regression model adjusted for age to determine whether the difference in ages of subjects in the standard and experimental group affected outcomes. There was still a statistically significant outcome when this was performed (p = 0.035) with an insignificant effect from age (p = 0.102). A Kaplan Meier curve was then conducted to confirm this finding (log rank p=0.0013).

Stage 2 analysis showed that the standard group subjects that switched to rTMS in Stage 2 had a significant reduction in negative outcomes compared to the standard group subjects who remained in pharmacologic treatment (McNemar Chi square, one tail, p=0.037). There was also no significant difference in positive outcomes between the treatment group in Stage 1 and the standard group subjects who switched to rTMS treatment in Stage 2 (p=0.64). This shows that
the positive outcome in the treatment group in Stage 1 was not due to individual differences between the subjects in this group and the standard group.

A secondary outcome of cocaine craving was logged during Stage 1, by patients rating a 0-10 visual analog scale. Craving scores were lower in the treatment group than the standard group during Stage 1 (p=0.038). (See Figure 1.); however, there was no significant difference in craving scores between groups during Stage 2.

Another secondary outcome, depression, was measured to ensure that a difference in depression between the groups did not contribute to the primary outcome and to assess the effects of treatment on depression. Participants completed a SCL-90 depression subscale before treatment and during Stage 1 and Stage 2. Analysis showed no significant difference in depression between the 2 groups before treatment. In Stage 1, both groups showed an improvement in depression symptoms with no significant difference between groups.

The limitation of this study is most notably a small sample study size of 32 subjects. This sample size is larger than the Bolloni et al study, however, still a relatively small group. The authors recognized this limitation, as well as noting that the open label design had a potential for bias. There is a potential concern that the disulfiram administered to deter alcohol consumption may have also contributed to a decrease in cocaine use in both groups during treatment. This, however, does not decrease the significance of the difference in positive outcomes between the two groups since both groups received disulfiram in equal amounts.

DISCUSSION

Cocaine use disorder is a prevalent issue on both an international and national scale. One hundred and seventy thousand people were in rehabilitation treatment for CUD in North America in 2014. From 2000-2016, deaths from cocaine overdose increased every year and totaled 10619
people, which does not include deaths from complications of chronic cocaine use. Most individuals with cocaine dependence are not able to recover without treatment. Even with treatment, 24% of patients relapse within one year. Cocaine’s ability to induce functional changes in the neuropathways of the prefrontal cortex that regulate impulsiveness and other executive functions make effective treatment particularly difficult. Due to the high mortality rate associated with cocaine use and no consistently proven effective treatments to date, the need for new treatment approaches is imminent.

rTMS is a noninvasive treatment that uses magnetic induction to create an intracranial electrical field significant enough to depolarize neurons, effectively stimulating them. In theory, stimulating the prefrontal cortex will ultimately reduce cocaine use behavior by “boosting” dopamine signaling in the brain. rTMS is an attractive treatment option due to its relatively short administration time, non-invasive nature, and mild adverse events. Since continued cocaine use holds such a high risk of mortality and social and economic dysfunction, the benefits of rTMS treatment far outweighs the adverse risks.

Results of the 2 studies compiled in this analysis show a statistically significant reduction in cocaine use in the subjects who received rTMS treatment compared to other treatment in both short and long term time spans. The Terraneo et al study compares current pharmacological treatment of cocaine use disorder to rTMS treatment. The Terraneo et al study showed lower cocaine use in the group receiving rTMS during the treatment stage and through a 3 month follow up period after treatment. The Bolloni et al study showed a decrease in cocaine use in the group receiving rTMS during treatment and during a longer follow up period of 6 months. This study shows that rTMS treatment may require less than 2 treatments a year.
The cost of treatment is a large barrier to CUD treatment since many individuals with CUD have lost their jobs and financial support. Most insurance companies cover rTMS for the treatment of depression since it is FDA approved for this condition, however, since the FDA has not approved rTMS for CUD, insurance coverage is variable for isolated CUD. More trials showing the effectiveness of rTMS treatment for CUD are required to gain FDA approval, and consequently insurance coverage. Many individuals with cocaine use disorder have co-morbid mental health disorders, including depression, which may indirectly allow them to have insurance coverage for rTMS. Without insurance, rTMS can range from $6 000 to $12 000. This may seem expensive until compared to the even greater cost of continued cocaine use and other current treatments for CUD. The out-of-pocket cost of inpatient CUD rehabilitation can be up to $100 000 making rTMS treatment a much cheaper alternative.

Repetitive transcranial magnetic stimulation is generally well tolerated with mild adverse effects. The most common side effects are mild headache in half of patients and mild scalp pain or facial twitching in a third of patients. These effects do not cause most patients to stop treatment and usually resolve with progressive treatments. The most serious risk is rare instances of rTMS induced seizures, although precautions can be taken to minimize this. 12

Psychotherapy is currently the most effective treatment for preventing relapse but there is a high rate of relapse if it is not augmented with another type of treatment. Studies on pharmacologic treatment for CUD show mixed results and high drop-out rates. The most common medications currently being used are methadone, dextroamphetamine, disulfram, and modanafil. These medications have adverse effects of their own13, making rTMS a good alternative.
Small sample size is the most notable limitation of both studies reviewed here, which led to less precision in the outcomes. The combined sample size of the Bolloni et al and Terraneo et al studies was only 42 subjects. The high attrition rate of the Bolloni et al study is another notable limitation that decreased the precision of this study. The study originally recruited 18 participants but lost 8 of them for various reasons before the data was analyzed, reducing the sample size by 44%. While the Terraneo et al study had a larger sample size and less attrition, the open-label study design increased the potential for biased outcomes. The Bollini et al study avoided selection bias by using a double-blind allocation sequence.

While both studies have significant limitations, their results are promising and their designs can be used to inform future trials. Further trials would ideally start with larger sample sizes and use a double-blinded model. Although both trials showed the effectiveness of rTMS in reducing short term cocaine use in the short term, trials with follow up periods longer than 6 months are needed to show whether rTMS has long-term effects on CUD.

There was only one study currently in progress that was found on the subject of rTMS and CUD when a search of the National Institute of Health clinical trials website was performed. This trial is a double-blinded RCT that will compare rTMS treatment to a sham rTMS treatment for subjects with CUD. Cocaine use will be the primary outcome, with secondary outcomes of depression, anxiety, psychopathological symptoms, and changes in sleep quality. Outcomes will be gathered at baseline, immediately after rTMS treatment, and at 2 weeks, 3 months, 6 months, and 12 months post treatment. The study is still in the recruitment phase. The results of this study will provide more evidence as to whether or not rTMS should come to the forefront of clinical treatment of CUD.
While both studies reviewed here have low to moderate levels of quality of evidence based on the GRADE criteria, the benefits of rTMS treatment seem to far outweigh the risk of adverse events of treatment and of continued cocaine use. Before a decision to receive rTMS treatment, patients should be informed of the limitations of research on rTMS and cocaine use and the adverse effects of rTMS, but also of the benefits of living a life free of cocaine use if rTMS treatment is successful.

CONCLUSION

While the studies assessing whether rTMS is effective for decreasing CUD use are few and have limitations, they show promising preliminary evidence to support rTMS as a treatment option. Larger studies with smaller attrition rates are required to prove the results found in the current studies. Head-to-head trials comparing other common treatments for CUD, such as different medication protocols, inpatient treatment, and psychotherapy, are required before the standard of care for individuals with CUD should include rTMS. It would also be beneficial to have studies done showing whether rTMS is effective as an adjunct therapy to current treatments. The study on this topic which is currently in process, with a larger sample size and double blinded RCT design, shows that there is continued interest in exploring this treatment. Before deciding on rTMS treatment, considerations such as insurance coverage and mild adverse effects must be reviewed with the individual. Due to the severe negative effects of cocaine use and the high risk of relapse with all current treatment options, rTMS should still be added to the list of options for treating CUD, especially for individuals who have failed other treatments.
Table 1: Quality Assessment of Reviewed Articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Bolloni et al</td>
<td>RCT</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Serious -</td>
<td>Unlikely</td>
<td>Moderate</td>
</tr>
<tr>
<td>Terraneo et al</td>
<td>RCT</td>
<td>Serious -</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Serious -</td>
<td>Unlikely</td>
<td>Low</td>
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- High attrition rate and/or small sample size
- Open label study with no allocation concealment

Table 2: Bolloni et al

<table>
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<tr>
<td>Gender (M/F)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Education (years)</td>
</tr>
<tr>
<td>Employed (yes/no)</td>
</tr>
<tr>
<td>Duration of cocaine dependence</td>
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<tr>
<td>Cocaine amount in hair (ng/mg)</td>
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Table 3: Terraneo et al

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<thead>
<tr>
<th>Participant Characteristics at Baseline</th>
<th>rTMS group (n=16)</th>
<th>Control group (n=16)</th>
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<tr>
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<td>43.5</td>
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<tr>
<td>Women</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Race: Caucasians (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Age of first cocaine use</td>
<td>26.69</td>
<td>24.06</td>
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<tr>
<td>Years of cocaine use</td>
<td>16.81</td>
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<tr>
<td>Cocaine use during the last month (days per week)</td>
<td>4.81</td>
<td>4.31</td>
</tr>
<tr>
<td>Cocaine use during the last month (grams per day)</td>
<td>1.81</td>
<td>1.75</td>
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<tr>
<td>Tobacco: smokes (%)</td>
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<td>56.25</td>
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<tr>
<td>Last use:</td>
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</tr>
<tr>
<td>Less than 24 h</td>
<td>37.50%</td>
<td>43.75%</td>
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<td>Between 24 and 48 h</td>
<td>18.75%</td>
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<td>More than 48 h</td>
<td>43.75%</td>
<td>31.25%</td>
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</table>
Figure 1: Terraneo et al

Cocaine Craving Scores
Terraneo et al

Craving Score

Days

Control group
rTMS Group
References


11. Dunlop B, Nemeroff C. The role of dopamine in the pathophysiology of depression. Vol 64. ; 2007:327-37. 10.1001/archpsyc.64.3.327.


