The Opiate Antagonist, Naltrexone, in the Treatment of Trichotillomania

Results of a Double-Blind, Placebo-Controlled Study

Jon E. Grant, MD, JD, MPH, Brian L. Odlaug, MPH,*† Liana R.N. Schreiber, BA,‡ and Suck Won Kim, MD‡*

Abstract: Trichotillomania (TTM) is characterized by repetitive hair pulling resulting in hair loss. Data on the pharmacological treatment of TTM are limited. This study examined the opioid antagonist, naltrexone, in adults with TTM who had urges to pull their hair. Fifty-one individuals with TTM were randomized to naltrexone or placebo in an 8-week, double-blind trial. Subjects were assessed with measures of TTM severity and selected cognitive tasks. Naltrexone failed to demonstrate significantly greater reductions in hair pulling compared to placebo. Cognitive flexibility, however, significantly improved with naltrexone ($P = 0.026$). Subjects taking naltrexone with a family history of addiction showed a greater numerical reduction in the urges to pull, although it was not statistically significant. Future studies will have to examine whether pharmacological modulation of the opiate system may provide promise in controlling pulling behavior in a subgroup of individuals with TTM.

Key Words: trichotillomania, opioid, impulsivity, hair pulling

(*J Clin Psychopharmacol* 2014;34: 134–138)

With an estimated prevalence of 1% to 4%,[1] trichotillomania (TTM) is a fairly common condition in which individuals repeatedly pull their hair (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [*DSM-5*]). Despite the promise from current treatments such as habit reversal therapy and medication,[2] treatments are not effective for all individuals with TTM, and so additional options are needed.

Trichotillomania seems to share phenomenological similarities to substance use disorders (SUDs).[3] Family history data suggest that individuals with TTM are significantly more likely than controls to have first-degree relatives with SUDs.[4] Individuals with TTM also exhibit difficulties with impulse inhibition, measured by the stop signal task (SST), as have individuals with SUDs.[5,6]

Given the possible clinical links between TTM and SUDs, medications effective in treating addictive disorders may be attractive candidates for the treatment of TTM. In fact, the opioid receptor antagonist, naltrexone, has previously been examined in the treatment of grooming behaviors in animals and in human TTM. Opioid antagonists reduce self-licking or self-chewing in 63% to 91% of dogs with acral lick dermatitis.[7,8] In a small (n = 17), 6-week, double-blind study, Christenson[2] examined the possible efficacy of naltrexone (50 mg/d) for adults with TTM. Subjects treated with naltrexone exhibited statistically significant improvement compared to placebo on 1 of 3 measures of hair pulling severity. More recently, an open-label study of naltrexone (50–100 mg/d) in 14 children with TTM reported that 11 (78.6%) exhibited significant improvement.[9] The efficacy of opioid antagonists in the treatment of repetitive behaviors has been proposed to involve opioidergic modulation of mesolimbic dopamine circuitry, leading to diminished urges to engage in the behavior.[10]

Because of the hypothesized mechanism of action of naltrexone and the previous findings of naltrexone's ability to reduce some aspects of hair pulling, the current study sought to enroll individuals with TTM who reported pulling secondary to urges. We hypothesized that naltrexone would reduce the severity of hair pulling urges and thereby improve behavior and patients' overall functioning.

MATERIALS AND METHODS

Men and women aged 18 to 75 years with a primary *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) diagnosis of TTM were recruited through newspaper advertisements and referrals. Only subjects who reported urges to pull (at least 50% of the time and a score of ≥1 on each of the first 3 items of the Massachusetts General Hospital Hair Pulling Scale [MGH-HPS]) were included. Exclusion criteria included (1) unstable medical illness; (2) current pregnancy or inadequate contraception; (3) thoughts of suicide; (4) history of bipolar disorder, dementia, or psychotic disorder; (5) past 12 months SUD; (6) previous treatment with naltrexone; (7) initiation of behavior therapy within the last 6 months; (8) initiation of a psychotropic medication within the last 3 months; and (9) current use of opiates.

Of 55 individuals screened for the study, 51 individuals (44% [86.3%] women; mean age, 32.7 [9.8] years) were randomized to naltrexone or placebo. Four individuals did not meet inclusion/exclusion criteria: 2 had bipolar disorder and 2 did not meet criteria for TTM. The 51 randomized subjects reported a mean age of TTM onset of 13.7 (7.2) years [range, 4–45 years]. Subjects pulled hair for a mean of 84.7 (53.4) minutes each day. Twenty-seven (52.9%) subjects reported a current comorbid disorder. Rates of comorbid disorders did not significantly differ between groups. Three (5.9%) had ongoing psychotherapy, and 17 (33.3%) were taking a psychotropic medication. Rates of medication use did not differ between treatment groups.

The University of Minnesota's institutional review board approved the study and the informed consent procedures. One investigator discussed potential risks of the study and alternative treatments. After complete description of the study, subjects provided written informed consent. This study was carried out

From the *Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL; †Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; and ‡Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN.

Received December 16, 2012; accepted after revision May 15, 2013.

Reprints: Jon E. Grant, MD, JD, MPH, Department of Psychiatry and Behavioral Neuroscience, University of Chicago, 5841 South Maryland Ave, MC 3077, Chicago, IL 60637 (e-mail: jongrant@uchicago.edu).

This research was internally funded.

ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000000037

in accordance with the Declaration of Helsinki. Data were collected from August 2008 to May 2012.

After screening, eligible subjects were randomized to 8 weeks of double-blind naltrexone or placebo in block sizes of 8, using computer-generated randomization with no clinical information in a 1:1 fashion. All eligible study subjects were started on naltrexone 50 mg/d or matching placebo for 2 weeks. At week 2, the dose was then increased to 100 mg/d and then increased again at week 4 to 150 mg/d.

Demographics and clinical features of TTM were assessed with a semistructured interview. Psychiatric comorbidity was assessed using the Structured Clinical Interview for *DSM-IV*.[11] Medical history, physical examination, and liver function tests were obtained. Subjects reported severity of TTM symptoms using the self-rated MGH-HPS, the primary outcome measure for the study.[12] Although a self-report measure, the MGH-HPS has generally been accepted as the primary outcome measure in studies of TTM.[2] Secondary measures included the clinician-administered National Institute of Mental Health Trichotillomania Symptom Severity scale[2] and the Clinical Global Impression (CGI)-Severity and Improvement scales.[13] Anxiety and depressive symptom severity were rated with the Hamilton Anxiety and Depression Rating Scales (HAM-A[14]; HAM-D[15]). Psychosocial functioning and quality of life were evaluated using the Sheehan Disability Scale (SDS[16]) and the Quality of Life Inventory (QoLI[17]).

Cognition was assessed using the intradimensional/extradimensional (IDED) shift task and the SST. The IDED task assesses aspects of learning and cognitive flexibility, which have been shown to be dependent on distributed frontostriatal circuitry including the dorsolateral prefrontal cortices.[18] The SST assesses the ability to suppress impulsive responses that are rendered prepotent, an ability dependent on distributed circuitry including the right inferior frontal gyrus and anterior cingulate cortices.[19]

Differences in response between placebo and naltrexone were adjusted for baseline disparities using the baseline score as a covariate. Primary and secondary measures were examined using analysis of variance modeling analyses (UNIANOVA, SPSS for Windows, Version 15.0, SPSS Inc, Chicago, IL). The baseline value of the measure being analyzed was used as a covariate.The difference in the overall level of posttreatment values, the main effect for treatment, was the test of primary interest. All subjects who returned for at least 1 postrandomization visit were included in the intent-to-treat population. Changes in cognitive performance between baseline and end of treatment were assessed using paired *t* tests. Effect sizes were also calculated using Cohen effect size index *d*. A *d* of 0.2 is considered a small effect size, 0.5 is medium, and 0.8 is large. Partial η^2 was also calculated, and greater than 0.2 is a large effect size, greater than 0.1 is a medium effect size, and greater than 0.05 is a small effect size. For each of the primary and secondary outcomes, observed power was also calculated.

RESULTS

There were no statistically significant imbalances regarding demographics or baseline TTM symptoms between treatment groups. The rate of study completion did not differ between groups ($P = 0.248$), with 20 (80%) of 25 subjects assigned to naltrexone, and 24 (92.3%) of 26 subjects assigned to placebo completing the 8-week trial. There were no statistically significant pretreatment differences between completers and noncompleters on any measures.

There were no significant differences observed for those assigned to naltrexone on the primary efficacy variable (MGH-HPS score) compared to placebo by study end point (Table 1),

TABLE 1. Treatment Responses of TTM Subjects Assigned to Placebo or Naltrexone (Intention-to-Treat)

	Baseline		End Point					
Variable[§]	Naltrexone (n = 25)	Placebo (n = 26)	Naltrexone (n = 25)	Placebo (n = 26)	*F* Test,* *df=1,48*	*P*	Effect Size[†] and CI	Partial $\eta^{2‡}$
MGH-HPS total score	16.24 (4.859) [2–23]	18.31 (3.792) [10–26]	12.21 (6.203) [0–21]	13.35 (4.749) [1–23]	0.026	0.873	0.221 [−2.54, 2.98]	0.001
NIMH scale total score	12.04 (3.963) [6–20]	12.88 (3.923) [6–20]	7.94 (4.835) [0–16]	8.73 (5.481) [1–20]	0.013	0.908	−0.138 [−2.53, 2.26]	0.000
SDS	10.88 (7.137) [0–24]	12.13 (6.409) [1–25]	6.74 (7.407) [0–30]	8.65 (6.811) [0–26]	0.475	0.494	−1.055 [−4.14, 2.03]	0.010
CGI Severity	4.48 (0.770) [3–6]	4.73 (0.827) [4–6]	3.44 (1.474) [1–6]	3.81 (1.167) [1–7]	0.385	0.538	−0.221 [−0.936, 0.494]	0.008
HAM-D	4.88 (4.428) [0–20]	4.38 (4.138) [0–17]	3.24 (3.574) [0–18]	2.58 (3.431) [0–16]	0.292	0.591	0.369 [−1.00, 1.74]	0.006
HAM-A	4.72 (3.182) [0–12]	4.31 (3.642) [0–13]	3.20 (2.309) [0–9]	2.23 (2.717) [0–13]	1.756	0.191	0.812 [−0.420, 2.04]	0.035
QoLI (*t*-score)[‖]	43.48 (10.239) [19–61]	45.12 (9.799) [16–63]	46.95 (10.146) [22–70]	45.46 (13.906) [0–64]	3.653	0.063	3.862 [−0.222, 7.95]	0.084

*Analysis of covariance with baseline as covariate.
[†]Cohen effect size based on adjusted differences in response between placebo and active (adjusted for baseline level).
[‡]Partial η^2 is the proportion of the effect plus error variance that is attributable to the effect.
[§]All variables are mean (SD) [range] unless otherwise indicated.
[‖]Missing observations on the QoLI t-score (end point)—only 24 placebo and 19 naltrexone observations for this analysis.
CI indicates confidence interval.

and the observed power was 0.053. Secondary measures also failed to reflect any significant differences between treatment groups. By study end point, 9 (36%) of those assigned to naltrexone were "much" or "very much" improved compared to 9 (34.6%) of those on placebo (Yates $\chi^2 = 0.04$; $df = 1$; $P = 0.920$). This placebo response rate is somewhat higher than rates seen in other studies (16%–17%).[4] Furthermore, the observed power for the CGI-Severity scale was 0.093, 0.051 for the NIMH scale, 0.462 for the QoLI, 0.104 for the SDS, and 0.083 and 0.255 for the HAM-D and HAM-A, respectively.

Pretreatment and posttreatment cognitive performances are found in Table 2. We found no significant between-group differences in motor inhibitory performance or for end point total errors adjusted. Because the equal variance assumption was clearly violated given the range of performance scores on the IDED task, we performed our analysis with a Welch *t* test (which does not assume equal variances between groups) and found that cognitive flexibility significantly improved in the naltrexone group compared to the placebo group ($t = 2.697$; $P = 0.028$). Within-group analysis also demonstrated that the naltrexone group significantly improved on cognitive flexibility from baseline to end point ($t = 2.329$; $P = 0.026$). Post hoc analyses examining whether particular components of the IDED task could be identified as markers in symptom improvement did not produce any meaningful results.

Previous research on naltrexone in other impulse control disorders has noted a preferential response for subjects reporting a family history positive for an alcohol use disorder (AUD) or SUD.[20] A total of 20 (39.2%) of the entire sample reported a first-degree family member with an AUD or SUD (n = 9 [36%] in the naltrexone group). We found that reduction in urges to pull from baseline to end point (using the first 3 items of the MGH-HPS) in the naltrexone group was numerically greater in those with a family history of an AUD or SUD, but not statistically significant ($t = 2.007$; $P = 0.057$; effect size = 0.837).

Overall, there were few adverse experiences, and sedation was the only adverse effect reported statistically more frequently in those taking naltrexone. Sedation, however, was quite mild, and there were no significant differences on cognitive tasks for those who reported sedation. Liver function testing—both change from baseline to end point and in the AST/ALT ratio—demonstrated no significant changes between or within groups.

DISCUSSION

This randomized, double-blind, clinical trial indicates that naltrexone is generally not more effective than placebo for TTM based on our primary and secondary outcome measures. The study hypothesis was not supported by the data, but post hoc analyses of the data yielded two potentially important findings. First, although it did not reduce urges in all TTM subjects, there is at least a preliminary suggestion that naltrexone may reduce urges to pull in individuals with TTM who also have a family history of substance addiction. Although this finding was not statistically significant, its effect size was large ($d = 0.837$). This potential response to naltrexone of reduced urges to pull (similar to its effects in reducing urges to drink alcohol or gamble) may imply that urges for reward reflect a transdiagnostic target for medication treatment, and that urges in those with a family history of addictions may share a common neurosubstrate which is independent of the target of the urges. Although preliminary, this finding may have potentially valuable clinical ramifications as naltrexone could be the preferred medication treatment for patients presenting with TTM who also endorse a family history

TABLE 2. Cognitive Task Performance at Baseline and End Point Between and Within Groups

Between-Group Analysis

	Naltrexone	Placebo			
Variable*	**Baseline**		**Test†**	***P***	**Effect Size (Cohen *d*)**
Total errors adjusted	21.0 (20.8) [7–68]	23.5 (20.3) [6–60]	0.409	0.685	0.126
Stop signal reaction time, ms	179.8 (59.6) [112.4–303.1]	169.3 (30.9) [122.6–232.0]	−0.736	0.466	−0.230
	End Point				
Total errors adjusted	8.4 (1.4) [7–12]	17.5 (18.5) [4–58]	1.894‡	0.066‡	0.631
Stop signal reaction time, ms	169.7 (47.6) [90.7–241.8]	161.1 (28.6) [119.1–243.2]	−0.700	0.488	−0.233

Within-Group Analysis

	Naltrexone				
Variable*	**Baseline**	**End Point**	**Test†**	***P***	
Total errors adjusted	21.0 (20.8) [7–68]	8.4 (1.4) [7–12]	−2.329	0.026	−0.811
Stop signal reaction time, ms	179.8 (59.6) [112.4–303.1]	169.7 (47.6) [90.7–241.8]	−0.536	0.596	−0.187
	Placebo				
	Baseline	**End Point**	**Test†**	***P***	
Total errors adjusted	23.5 (20.3) [6–60]	17.5 (18.5) [4–58]	−1.047	0.301	−0.312
Stop signal reaction time, ms	169.3 (30.9) [122.6–232.0]	161.1 (28.6) [119.1–243.2]	−1.075	0.289	−0.324

*All variables are mean (SD) [range] unless otherwise indicated.

†*t* test assuming equal variance unless otherwise indicated.

‡*t* test run assuming unequal variance is $t = 2.351$, $P = 0.028$.

of substance addiction. Additional trials examining this particular question are warranted.

The second important finding from this study was that neurocognitive testing indicated significant improvements in cognitive flexibility after treatment with naltrexone. Cognitive flexibility may represent a promising target for treatment in some individuals with TTM. Individuals with problems in cognitive flexibility may have difficulties disengaging attention from a task or resolving interference from previous stimuli or tasks. Cognitive inflexibility might therefore prevent individuals from shifting from one thought to another and thus lock them in to a specific behavior. This seems to reflect what is described clinically in TTM—for example, people start pulling hair and even as they notice bald spots, they cannot stop the behavior as they become fixated in ridding themselves of certain types of hairs (coarse, kinky, etc). Complicating our understanding of naltrexone's effects on cognitive flexibility, however, is recent research indicating that the μ-opioid system within the anterior cingulate cortex, ventromedial, and dorsolateral prefrontal cortices may play a pivotal role in the personality trait of harm avoidance.[21] Future studies will have to examine what may be a complicated interplay between personality traits, cognitive dysfunction, and hair pulling behavior. In light of this potentially complicated neurobiological picture of a presumed simple behavior, it is not surprising that previous studies have elicited conflicting neuropsychological profiles for individuals with TTM with one study demonstrating impaired cognitive flexibility,[22] whereas another found intact set shifting.[5] Nonetheless, our result of improved cognitive flexibility in the naltrexone-treatment group only, and not the placebo group, indicates that naltrexone may have cognitive benefits for some TTM subjects even if not directly related to the hair pulling behavior. In previous research, naltrexone has demonstrated improvement in attentional set-shifting cognition in animal models, further demonstrating the potential benefit of this class of medication for deficits in cognitive flexibility.[23] Whether a subgroup of subjects with TTM who have cognitive flexibility problems would benefit preferentially from naltrexone awaits further research in larger samples.

Several noteworthy limitations exist in this clinical trial. First, the sample size was likely too small to detect notable differences in treatment effect. In fact, post hoc power analyses demonstrate that based on the standard deviations and the r^2 from the data (with a specified modest effect of a 1-U difference between groups), a sample of approximately 179 subjects in each group would be needed. A larger study, powered to perform subgroup analyses, may ultimately allow for greater clarification of whether certain subgroups of TTM subjects would benefit from naltrexone. Second, subjects did not provide genetic samples in this study. Genetic research in alcoholism has demonstrated that individuals with 1 or 2 copies of the Asp40 allele (SNP in the gene encoding the μ-opioid receptor OPRM1) treated with naltrexone had lower rates of relapse than those homozygous for the Asn40 allele.[24] Whether genetic markers in TTM could reflect a preferential response to naltrexone awaits future studies. Third, we did not interview first-degree family members of subjects directly, relying only on subject report. Previous studies have indicated biases involved with indirect interviews about family history.[25] Future research should aim to directly interview first-degree relatives of subjects to substantiate psychiatric histories within the family. Fourth, a potential limitation of the study is that the sample included only those participants who reported the presence of hair pulling urges and therefore may not be representative of a larger population of individuals with TTM who pull out their hair automatically. Finally, given that sedation was more common among those assigned to naltrexone, it is possible that this affected the study blind. Because nausea was the primary adverse effect subjects were warned about and because the sedation was generally mild, however, we expect that sedation was unlikely to affect subject or rater awareness of assignment.

This study indicates that although naltrexone is not beneficial for individuals with TTM as a whole, it may be a potentially promising treatment to reduce urges to pull in those with pronounced cognitive inflexibility or those with a family history positive for substance addiction. Given the limited treatment options available for TTM and relatively high population prevalence of the disorder, this study provides additional information for subjects and family members coping with this condition. It also serves to encourage future pharmacological research in an effort to find a first-line treatment for TTM.

AUTHOR DISCLOSURE INFORMATION

Dr Grant has received research grants from NIMH, NIDA, a Center for Excellence in Gambling Research grant from the National Center for Responsible Gaming (NCRG), Roche, Transcept, Forest, and Psyadon Pharmaceuticals, and the University of South Florida. He receives yearly compensation from Springer Publishing for acting as Editor-in-Chief of the Journal of Gambling Studies. He has received royalties from Oxford University Press, American Psychiatric Publishing, Inc, Norton Press, and McGraw Hill. Mr Odlaug has received research grants from the Trichotillomania Learning Center, has consulted for Lundbeck Pharmaceuticals, and has received honoraria and royalties from Oxford University Press. Ms Schreiber and Dr Kim report no conflicts of interest.

REFERENCES

1. Mansueto CS, Rogers KE. Trichotillomania: epidemiology and clinical characteristics. In: Grant JE, Stein DJ, Woods DW, eds. *Trichotillomania, Skin Picking, & Other Body-Focused Repetitive Behaviors*. Washington, DC: APPI; 2012:3–20.
2. Christenson GAH. The assessment and treatment of trichotillomania. In: Grant JE, Potenza MN, eds. *The Oxford Handbook of Impulse Control Disorders*. New York, NY: Oxford University Press; 2012:313–333.
3. Grant JE, Odlaug BL, Potenza MN. Addicted to hair pulling? How an alternate model of trichotillomania may improve treatment outcome. *Harv Rev Psychiatry.* 2007;15(2):80–85.
4. Schlosser S, Black DW, Blum N, et al. The demography, phenomenology, and family history of 22 persons with compulsive hair pulling. *Ann Clin Psychiatry.* 1994;6(3):147–152.
5. Chamberlain SR, Fineberg NA, Blackwell AD, et al. Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. *Am J Psychiatry.* 2006;163(7):1282–1284.
6. Li CS, Huang C, Yan P, et al. Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men. *Neuropsychopharmacology.* 2008;33(8):1798–1806.
7. Dodman NH, Shuster L, White SD, et al. Use of narcotic antagonists to modify stereotypic self-licking, self-chewing, and scratching behavior in dogs. *J Am Vet Med Assoc*. 1988;193(7):815–819.
8. White SD. Naltrexone for treatment of acral lick dermatitis in dogs. *J Am Vet Med Assoc*. 1990;196(7):1073–1076.
9. De Sousa A. An open-label pilot study of naltrexone in childhood-onset trichotillomania. *J Child Adolesc Psychopharmacol*. 2008;18(1):30–33.
10. Ikemoto S. Brain reward circuitry beyond the mesolimbic dopamine system: a neurobiological theory. *Neurosci Biobehav Rev.* 2010;35(2):129–150.
11. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV-Patient Edition (SCID-I/P, Version 2.0)*. New York, NY:

Biometrics Research Department, New York State Psychiatric Institute; 1995.

12. Keuthen NJ, O'Sullivan RL, Ricciardi JN, et al. The Massachusetts General Hospital (MGH) Hairpulling Scale: 1. development and factor analyses. *Psychother Psychosom*. 1995;64:141–145.
13. Guy W. *ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education & Welfare (ADM) 76–338*. Rockville, MD: National Institute of Mental Health; 1976.
14. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32:50–55.
15. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56–62.
16. Sheehan DV. *The Anxiety Disease*. New York, NY: Scribner's; 1983.
17. Frisch MB, Cornell J, Villanueva M. Clinical validation of the Quality of Life Inventory: a measure of life satisfaction for use in treatment planning and outcome assessment. *Psychol Assess*. 1993;4(1):92–101.
18. Owen AM, Roberts AC, Polkey CE, et al. Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia*. 1991;29(10):993–1006.
19. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. *Trends Cogn Sci*. 2004;8(4):170–177.
20. Grant JE, Kim SW, Potenza MN, et al. Predicting response to opiate antagonists and placebo in the treatment of pathological gambling. *Psychopharmacoogyl (Berl)*. 2008;200:521–527.
21. Tuominen L, Salo J, Hirvonen J, et al. Temperament trait Harm Avoidance associates with μ-opioid receptor availability in frontal cortex: a PET study using [(11)C]carfentanil. *Neuroimage*. 2012;61(3):670–676
22. Grant JE, Odlaug BL, Chamberlain SR. A cognitive comparison of pathological skin picking and trichotillomania. *J Psychiatr Res*. 2011;45(12):1634–1638.
23. Rodefer JS, Nguyen TN. Naltrexone reverses age-induced cognitive deficits in rats. *Neurobiol Aging*. 2008;29(2);309–313.
24. Oslin DW, Berrettini W, Kranzler HR, et al. A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. *Neuropsychopharmacology*. 2003;28(8):1546–1552.
25. Roy MA, Walsh D, Prescott CA, et al. Biases in the diagnosis of alcoholism by the family history method. *Alcohol Clin Exp Res*. 1994;18(4):845–851.