



ORIGINAL INVESTIGATION

A double-blind, placebo-controlled trial of topiramate for pathological gambling

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Abstract

Objectives. Pathological gambling (PG) is an impulse control disorder characterized by recurrent gambling thoughts and behaviours that impair social functioning. Earlier studies suggested that topiramate may be effective in treating some impulse control disorders. We conducted the first randomized, controlled trial of topiramate in PG. **Methods.** PG patients were randomized to topiramate ($N = 20$) or placebo ($N = 22$) in this 14-week, double-blind, placebo-controlled, parallel-group trial. The primary outcome measure was change in the obsessions subscale of the Yale-Brown Obsessive-Compulsive Scale Modified for Pathological Gambling. **Results.** Mixed regression models (time [weeks] \times treatment) revealed no significant treatment effect of topiramate on the primary or secondary outcome measures. The most statistically robust findings involved reducing the Barratt Impulsiveness Scale (BIS) total score and Motor and Non-Planning subscale scores, for which topiramate outperformed placebo at merely a trend level ($P < 0.1$). **Conclusions.** The observed trend in BIS score reductions may warrant further investigation to study whether topiramate reduces clinically important impulsivity in PG. Treatment studies with larger samples and less stringent exclusion criteria are needed to produce results that can be generalized to pathological gamblers in the community.

Key words: pathological gambling, topiramate, impulsivity, impulse control disorder, placebo-controlled

Introduction

Pathological gambling (PG) has a prevalence of about 1%, and co-morbid psychiatric conditions are common (Petry et al. 2005; Cunningham-Williams et al. 2005, 2007; Kessler et al. 2008). Features of PG include impulsivity, recurrent gambling despite deleterious consequences, craving, and other aspects of addiction (Lesieur 1998; Muelleman et al. 2002; Sood et al. 2003; Dickson-Swift et al. 2005).

Although no drugs have formal indications for PG, controlled pharmacological trials provide direction (Hollander et al. 2008). Studies utilizing opioid antagonists have produced promising results (Kim 1998; Kim and Grant 2001; Kim et al. 2001; Grant et al. 2006, 2008, in press), while controlled trials of serotonin reuptake inhibitors have generated mixed findings (Hollander et al. 2000, 2005; Blanco et al. 2002; Kim et al. 2002; Grant et al. 2003, in press;

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Saiz-Ruiz et al. 2005). Treatment of PG with mood stabilizers has been suggested, especially when bipolar mood symptoms are present (Berlin 2008; Hollander et al. 2008). However, two placebo-controlled trials of the atypical antipsychotic olanzapine were negative (Fong et al. 2008; McElroy et al. 2008).

Topiramate has been superior to placebo in treating several disorders characterized by impulsivity and craving/urges: bulimia nervosa (Hoopes et al. 2003), binge eating disorder (Carter et al. 2003; McElroy et al. 2003; McElroy et al. 2007), alcohol dependence (Johnson et al. 2003, 2004, 2007; Shinn and Greenfield 2010), and cocaine dependence (Kampman et al. 2004; Karila et al. 2008; Reis et al. 2008). Since these disorders share with PG features of impulsivity and craving (McIntyre et al. 2002; Carter et al. 2003; McElroy et al. 2003; McElroy and Keck 2009), topiramate may be effective in reducing impulsivity and urges to gamble in PG.

A case study (Nicolato et al. 2007), a randomized, blind-rater study (Dannon et al. 2005), and a naturalistic, long-term follow-up study (Dannon et al. 2007) suggest that topiramate may be effective for PG. The present study is the first placebo-controlled study to test this hypothesis. The present study also differs from earlier topiramate trials by including clinician-rated scales and both male and female subjects.

We hypothesized that topiramate would be superior to placebo on: (1) the primary outcome measure: the obsessions subscale of the Yale-Brown Obsessive Compulsive Scale modified for PG (PG-YBOCS); and (2) secondary outcome measures related to gambling behaviours (e.g., PG-YBOCS compulsions subscale scores) and impulsivity (as assessed by the Barratt Impulsivity Scale (BIS-11)).

Methods

This was a 14-week, five-centre, randomized, double-blind, placebo-controlled, flexible-dose study of topiramate in outpatients aged 17–70 years with DSM-IV-TR diagnosed PG. The study recruited PG subjects primarily through community advertisements (e.g., newspapers) and targeted advertisements in casinos. Eligible participants were enrolled between 26 October 2005 and 23 May 2008 and met the following criteria: current DSM-IV-TR diagnosis of PG supported by the Structured Clinical Interview for Pathological Gambling (Grant et al. 2004) (meeting \geq five inclusionary criteria and not meeting the exclusion criterion of being better accounted for by manic behaviour); a score of \geq 4 (moderately ill) on the Clinical Global Impression Scale – Severity (CGI-S) (Guy 1976); a severity score of \geq 5 on the South Oaks Gambling Screen;

(Lesieur and Blume 1987); a score of \geq 2 for item 1 on the Gambling Symptom Assessment Scale (G-SAS) (“If you had urges to gamble during the past WEEK, on average, how strong were your urges?”); and, a minimum score of \geq 10 on the obsessions subscale of the PG-YBOCS (Pallanti et al. 2005).

Exclusion criteria were: current DSM-IV-TR Axis I psychiatric disorder (other than PG), as determined by the SCID-I/P (First et al. 2002), that required treatment in the investigator’s judgment; a personality disorder (e.g., schizotypal or borderline) considered by the investigator to be likely to interfere with assessment or compliance with treatment (as determined by clinical interview); participation in formal psychotherapy for PG within the past 4 weeks, with the exception of attending Gamblers Anonymous; commencement of formal psychotherapy within the past 3 months; a score of \geq 15 on the Young Mania Rating Scale (YMRS; (Young et al. 1978)); or, a score of \geq 24 on the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg 1979). These YMRS and MADRS cut-off scores permit only mild depressive and manic symptoms. A YMRS score of 16 is the standard entry criterion for acute mania studies. A MADRS score of 24 is equivalent to a Hamilton Rating Scale for Depression-17 (HAM-D-17; (Hamilton 1960) of 16, a standard enrolment criterion for acute depression studies. Since symptoms of depression and mania are common in PG, we attempted to strike a balance between clinical realities and the need for pure and homogeneous study samples, and thus allowed sub-syndromal concurrent depression and mania, but excluded full episodes.

Subjects taking psychotropic medication or having positive urine drug screens were excluded, as were pregnant or lactating women. Subjects treated previously with topiramate were excluded. The study was approved by the institutional review boards at each site, and all subjects signed written informed consent prior to participation.

Subjects were randomized in a 1:1 ratio to topiramate or placebo treatment. Following the baseline visit, participants underwent a 6-week titration period to 300 mg/day or the maximum tolerated dose (Table I), followed by an 8-week maintenance period. The study medication consisted of 25 or 100 mg of topiramate or matching placebo in identical-appearing tablets. The target dose of 300 mg/day was chosen to replicate the doses that were found to be both effective and well-tolerated in studies of binge eating disorder and alcohol abuse (Leombruni et al. 2009; Shinn and Greenfield 2010). Subjects had to maintain a minimum dose of 50 mg/day to remain in the study. At the conclusion of the 14 weeks, study medication was tapered over a 7-day period.

Table I. Double-blind topiramate/placebo dosing.

Study day	Study medication		Total daily dose	
	25 mg tablets (Bottle A)	100 mg tablets (Bottle B)	Topiramate	Placebo
1–7	1 tablet h.s.		25 mg	matching
8–14	1 tablet b.i.d. (AM/PM)		50 mg	tablet(s)
15–21	2 tablets b.i.d. (AM/PM)		100 mg	
22–28	3 tablets b.i.d. (AM/PM)		150 mg	
29–35		1 tablet b.i.d. (a.m./p.m.)	200 mg	
36–42		1 tablet (a.m.)/2 tablets (p.m.)	300 mg	

The primary outcome measure was change in the obsessions subscale of the PG-YBOCS. The PG-YBOCS measures the severity and change in severity of PG symptoms (i.e. thoughts/urges and behaviours) and has been shown to be reliable and valid and correlate with global severity and South Oaks Gambling Screen scores (Pallanti et al. 2005).

We chose the obsessions subscale of the PG-YBOCS as the a priori primary outcome measure for two reasons. First, we hypothesized that topiramate might preferentially affect gambling-related thoughts and urges as gambling behaviours might be influenced by external factors, such as access to financial resources.

Secondary outcome measures included scores on: (1) the PG-YBOCS (total and compulsion component); (2) Barratt Impulsivity Scale (BIS-11 (Patton et al. 1995), a 30-item, four-point, validated measure, widely used to assess impulsivity in three domains (attentional/cognitive [rapid shifts and impatience with complexity], motor [impetuous action], and non-planning [lack of future orientation]); (3) G-SAS (Kim et al. 2001), a 12-item self-rated scale that assesses the change in gambling urges, thoughts, and behaviour; (4) the YMRS; (5) the MADRS; (6) Hamilton Anxiety Rating Scale (HARS; Hamilton 1959); (7) Sheehan Disability Scale (Sheehan 1983); (8) Affective Lability Scale (Harvey et al. 1989); and (9) Clinical Global Impression – Improvement (CGI-I) scale. Responders were defined as having a CGI-I score = 1 or 2, and non-responders a score >2 at their week 10 evaluations. We used two-level mixed regression analyses to test the time (coded as weeks) \times treatment (coded as Placebo = 0, Treatment = 1) interaction. All randomized patients with available data ($N = 41$) were included in the intent-to-treat analyses of the primary aim, as reflected in their scores on both the primary and secondary outcome measures (see Figure 1).

Our power calculations were based on the results of a previous study reporting a difference between an active treatment and placebo of 2.1 units on the PG-YBOCS scale, which is comparable to a mean difference between groups of approximately 10%

(Hollander et al. 1998). The observed within treatment group standard deviation of this change was approximately 4.0 units. With the planned sample size of 120 subjects, to achieve a power of 0.80 with the two-tailed α set at $P \leq 0.05$ would require the study's effect size to be 0.525 (Cohen's d), conventionally described as moderate.

Results

Forty-two subjects were randomized to topiramate ($N = 20$) or placebo ($N = 22$). Subjects' mean age was 47.5 years ($SD = 9.5$), and 23 (55%) were women. The two groups did not differ significantly on demographic characteristics or baseline or end-point measures (see Tables II and III). The highest mean weekly dose of placebo reached before taper was 252.27 mg/day ($SD = 99.68$ mg); for topiramate this dose was 222.50 mg/day ($SD = 108.49$ mg).

There were 27 completers and 15 non-completers. Non-completers included nine placebo-group subjects (one adverse event, five lost to follow-up, three subject choice), and six topiramate-group subjects (two adverse events, one lost to follow-up, two subject choice, and one lack of efficacy). No between-group difference was observed in non-completion frequency ($P = 0.531$).

At visit 10, 31 of the 42 (74%) subjects received a CGI-I rating. Twenty subjects (65%) were responders (CGI-I = 1 or 2), with no between-treatment-group difference observed (Fisher exact (two-tail) $P = 1.0$; odds ratio = 1.25). Since this analysis did not include the 11 subjects who missed visit 10, an intent-to-treat analysis was performed. Based on available data, we used mixed regression to estimate an intercept and a linear slope for the 11 subjects, estimate visit-10 CGI scores, and classify subjects as responders or non-responders. (One subject dropped out before any CGIs were obtained, preventing an estimate of the visit-10 score for this subject, thus giving an intent-to-treat N of 41 for the CGI analyses). The difference in response rates between the treatment and placebo groups remained insignificant ($P = 0.536$; odds ratio = 1.650).

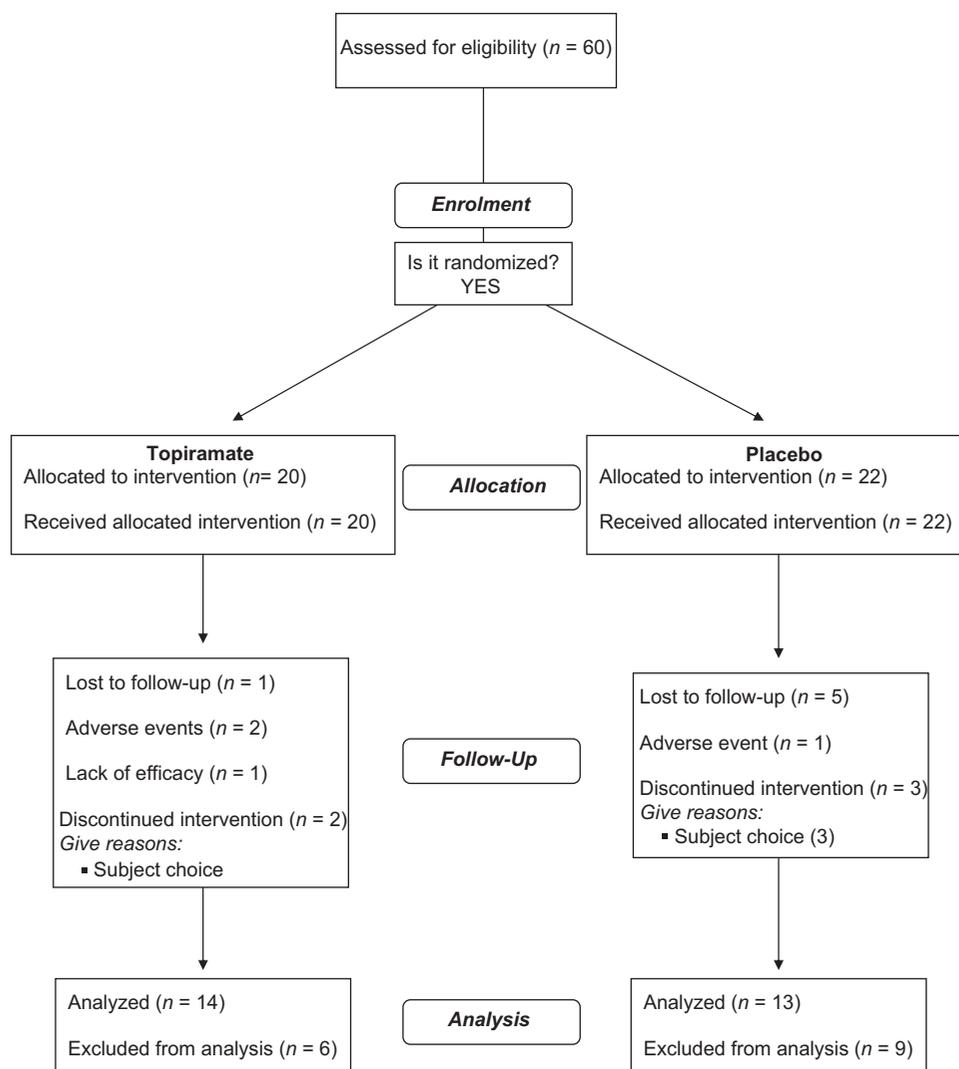


Figure 1. CONSORT flow diagram.

Consistent with the completer analysis, the two groups did not differ significantly at endpoint (weeks × treatment) on the PG-YBOCS obsessions subscale

Table II. Demographic characteristics.

	Number of participants		
	Topiramate (n = 20)	Placebo (n = 22)	P value (Fisher exact test)
<i>Gender</i>			
Male	12	7	0.12
Female	8	15	
<i>Ethnicity</i>			
White	11	16	0.50
Black	7	5	
Other	2	1	
Age, mean (SD)	50.45 (10.44)	44.91 (8.01)	0.59 (t-test)
<i>Smoking</i>			
Smoker	8	15	0.12
Non-smoker	12	7	

($t = -0.284$, $df = 27.931$, $P = 0.779$). In addition, no significant treatment effect was seen for the secondary outcome measures: PG-YBOCS total ($t = -0.283$, $P = 0.779$) and compulsion scores ($t = -0.049$, $P = 0.961$), G-SAS ($t = 0.490$, $P = 0.628$), HARS ($t = 0.639$, $P = 0.528$), MADRS ($t = 1.142$, $P = 0.262$), YMRS ($t = 0.826$, $P = 0.414$), and CGI-I ($P = 0.536$, odds ratio = 1.650).

The most statistically robust differences between the active treatment and placebo groups, though still merely trends, were seen on the BIS-11. At week 14, the active treatment group showed trends toward greater decreases on the Motor ($t = -1.77$, $P = 0.087$) and Non-Planning ($t = -1.83$, $P = 0.077$) subscales and on the Total Score ($t = -1.70$, $P = 0.099$) compared to the placebo group, whereas no trend difference was seen on the Attention subscale ($t = -0.508$, $P = 0.615$). The parameter estimates across the 14 weeks for the active treatment group showed a greater predicted drop on the Motor subscale of

Table III. Baseline and endpoint outcome measures (Means, SDs, and *P* values).

	Baseline Mean (SD)			Endpoint Mean (SD)		
	Topiramate (<i>n</i> = 20)	Placebo (<i>n</i> = 22)	<i>P</i> value*	Topiramate (<i>n</i> = 20)	Placebo (<i>n</i> = 22)	<i>P</i> value*
<i>PG-YBOCS</i>						
Obsessions	12.65 (2.08)	12.95 (2.24)	0.651	6.17 (3.28)	7.62 (3.66)	0.257
Compulsions	11.10 (3.26)	12.27 (2.91)	0.225	5.28 (4.71)	6.92 (4.48)	0.336
Total	23.75 (4.80)	25.23 (4.89)	0.330	11.44 (7.81)	14.54 (7.79)	0.285
<i>BIS</i>						
Attentional	18.18 (4.03)	18.00 (4.57)	0.894	16.83 (4.30)	17.41 (5.13)	0.738
Motor	25.35(3.83)	25.27 (4.86)	0.955	22.32 (3.37)	23.85 (5.05)	0.319
Non-planning	30.07 (3.91)	28.90 (5.50)	0.436	29.00 (4.04)	30.38 (6.10)	0.452
Total	73.59 (9.22)	72.16 (12.50)	0.679	68.14 (8.30)	71.66 (14.54)	0.400
<i>G-SAS</i>	31.95 (7.41)	35.73 (7.85)	0.118	19.94 (9.18)	23.00 (11.55)	0.419
<i>HARS</i>	6.35 (3.62)	7.68 (5.25)	0.357	4.94 (5.22)	5.31 (6.99)	0.869
<i>MADRS</i>	8.70 (8.29)	9.54 (6.62)	0.716	7.06 (8.54)	4.69 (5.74)	0.394
<i>SDS</i>	13.00 (6.63)	15.82 (7.30)	0.199	7.80 (7.26)	10.50 (8.42)	0.838
<i>YMRS</i>	3.85 (3.65)	3.95 (3.84)	0.916	2.61 (2.97)	1.6154 (2.02)	0.305
<i>ALS Total</i>	1.37 (.62)	1.28 (.74)	0.698	No endpoint assessment	No endpoint assessment	na

*None of these differences reached statistical significance using independent samples *t*-tests (two-tailed).

PG-YBOCS, Yale-Brown Obsessive Compulsive Scale modified for PG; G-SAS, Gambling Symptom Assessment Scale; HARS, Hamilton Anxiety Rating Scale; MADRS, Montgomery—Asberg Depression Rating Scale; SDS, Sheehan Disability Scale; YMRS, Young Mania Rating Scale; ALS, Affective Liability Scale.

2.11 points (14×-0.151), the Non-Planning subscale of 2.12 points (14×-0.158), and the Total score of 5.19 points (14×-0.371) compared to the placebo group. Thus, we followed up the marginally significant interaction effect on the Motor and Non-Planning scales with a “simple effects” analysis by looking, post hoc, at just the topiramate group. We combined the parameter estimate of the overall effect of weeks and the additional drop for the topiramate group (interaction term) to determine if the total drop in this treatment group was significant. Within just the topiramate group the drop on both the Motor and Non-planning scales was statistically significant. For the Motor Subscale, the topiramate group had a significant overall drop of -0.22 points/week or 3.08 points (14×-0.22) from week 0 to week 14 ($P = 0.000$), and for the Non-Planning scale they had a drop of -0.09 /week or a predicted drop of 1.26 points (14×-0.09) ($P = 0.043$).

Adverse events

A total of 28 (66%) of the 42 participants in both treatment groups reported at least one adverse event (AE). The total number of AEs reported was 101. Most AEs were mild to moderate in severity. The most common AEs reported were tiredness (seven), headache (five), nausea (three), and shoulder pain (three). Fifty-two (51.5%) of the 101 AEs were reported by the placebo group and 49 (48.5%) by the active drug group. There was no relation between treatment and severity of the AEs (Fisher

Exact test $P = 0.325$), between treatment and prevalence of AEs ($P = 0.536$), or between giving concomitant medication for an AE and treatment group ($P = 0.659$). However, drug dose reduction occurred more frequently in the active drug group than in the placebo group in response to the AEs ($P < .001$).

Discussion

For both primary and secondary outcome measures, and contrary to our hypotheses, topiramate was not superior to placebo in the treatment of PG. This study has several important limitations, with the most serious being the small sample size and the exclusion criteria that make the sample unrepresentative of PG in the community. Recruitment, and ultimately, funding issues reduced to 42 the number of subjects enrolled in the study. Recruitment was severely hampered by the exclusion criteria that prevented potential subjects with comorbid psychiatric or medical conditions from being enrolled. The resulting slow pace of enrolment led to the exhaustion of available funds (to support staffing costs) well before the planned number of subjects with PG alone could be found.

Given its small sample size, the study may be underpowered to detect smaller, and yet clinically meaningful, differences in topiramate effects on PG symptoms. Whereas the intended sample size of 120 subjects would have had a power of 0.80 to detect

an effect size of 0.525, the reduced sample would not detect (with this power) any effect size smaller than 0.75. Thus, interpreting the findings as negative rather than as indeterminate must be done with considerable caution. In addition to the effects of the exclusion criteria on the representativeness of the subjects, treatment-seeking PG subjects may not represent those in the community, thus producing selection bias. The assignment to treatment or placebo group may have been unbalanced with regard to cognitive or other unmeasured factors influencing gambling propensity, and some co-occurring disorders may have been missed at screening. Additionally, the study duration was short.

The most statistically robust between-group difference on primary or secondary outcome measures was a trend difference on the BIS-11, particularly with respect to motor and non-planning impulsivity. Because an earlier study found that measures of impulsivity (assessed by the Eysenck Impulsiveness Questionnaire) correlated with severity of gambling (assessed by the PG-YBOCS) and that decreases in gambling symptoms during treatment correlated with decreases in impulsivity (Blanco et al. 2009), and because topiramate has been observed to decrease BIS scores in other conditions exhibiting substantial impulsivity, such as binge eating disorder (McElroy et al. 2007), perhaps topiramate should be investigated further as a treatment for elevated impulsivity.

Preliminary data suggest that anticonvulsant drugs like topiramate may be effective for the treatment of impulsivity across a range of psychiatric disorders, including cluster B personality disorders and impulse control disorders (Berlin 2008). However, given that even without correcting for multiple comparisons, our findings with respect to impulsivity measures only trended towards significance, and no significant effect on PG symptoms was observed, the current study of topiramate's effectiveness in PG should be considered negative or indeterminate on all primary and secondary outcome measures. The more stringent interpretation is to consider the results indeterminate because of limited statistical power brought about by the smaller than intended sample size.

Although our findings begin to suggest that topiramate is not effective in the treatment of PG, future studies targeting PG subjects with high motor and non-planning impulsivity warrant consideration. In addition, future studies should consider utilizing less stringent exclusion criteria.

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Statement of Interest

Heather Berlin, PhD, MPH, Stefano Pallanti, MD, PhD, Daphne Simeon, MD, and Ashley Braun, BA, have no potential conflicts of interest. Lorrin Koran, MD's, potential conflicts of interest relevant to the time frame of the paper were Forest Pharmaceuticals, Speakers' Bureau; Eli Lilly, research grant; Sepracor, research grant; and Jazz Pharmaceuticals, Consultant. Eric Hollander, MD, has consulted and received research grants from Ortho-McNeil, Abbott, and Solvay. Timothy Fong, MD, received research support from Ortho McNeil, NIDA (K23 Career Development Award) and the Annenberg Foundation, and participated in the Speaker's Bureaus of with Pfizer, Eli Lilly and Reckitt-Benckiser. Susan McElroy, MD, is a consultant to or member of the scientific advisory boards of Eli Lilly, Ortho-McNeil (during the time the study was conducted), and Schering-Plough. She is a principal or co-investigator on studies sponsored by the above companies and Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Forest, GlaxoSmithKline, Jazz, Marriott Foundation, National Institute of Mental Health, OREXIGEN, Shire, and Takeda Pharmaceutical Company Ltd. She is also an inventor on United States Patent No. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and along with the patent's assignee, University of Cincinnati, Cincinnati, Ohio, has received payments from Johnson & Johnson, which has exclusive rights under the patent. Marc N. Potenza, MD, PhD, has consulted for Boehringer Ingelheim; has financial interests in Somaxon; has received research support from the National Institutes of Health, Veteran's Administration, Mohegan Sun Casino, and Forest Laboratories, Ortho-McNeil, Oy-Control/Biotie and Glaxo-SmithKline pharmaceuticals; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; has consulted for law offices and the federal public defender's office in issues related to impulse control disorders; has performed grant reviews for the National Institutes of Health and other agencies; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; has generated books or book chapters for publishers of mental health texts; has edited for journals; and has provided clinical care in the

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