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ORIGINAL INVESTIGATION

Memantine shows promise in reducing gambling severity and cognitive inflexibility in pathological gambling: a pilot study

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Abstract
Rationale Although pathological gambling (PG) is relatively common, pharmacotherapy research for PG is limited. Memantine, an N-methyl D-aspartate receptor antagonist, appears to reduce glutamate excitability and improve impulsive decision making, suggesting it may help individuals with PG.
Objective This study sought to examine the safety and efficacy of Memantine in PG.
Methods Twenty-nine subjects (18 females) with DSM-IV PG were enrolled in a 10-week open-label treatment study of memantine (dose ranging from 10 to 30 mg/day). Subjects were enrolled from January 2009 until April 2010. Change from baseline to study endpoint on the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS) was the primary outcome measure. Subjects underwent pre- and post-treatment cognitive assessments using the stop-signal task (assessing response impulsivity) and the intra-dimensional/extra-dimensional (ID/ED) set shift task (assessing cognitive flexibility).
Results Twenty-eight of the 29 subjects (96.6%) completed the 10-week study. PG-YBOCS scores decreased from a mean of 21.8±4.3 at baseline to 8.9±7.1 at study endpoint ($p<0.001$). Hours spent gambling per week and money spent gambling both decreased significantly ($p<0.001$). Subjects also demonstrated a significant improvement in ID/ED total errors ($p=0.037$) at study endpoint. The mean effective dose of memantine was 23.4±8.1 mg/day. The medication was well-tolerated. Memantine treatment was associated with diminished gambling and improved cognitive flexibility.
Conclusions These findings suggest that pharmacological manipulation of the glutamate system may target both gambling and cognitive deficits in PG. Placebo-controlled, double-blind studies are warranted in order to confirm these preliminary findings in a controlled design.

Keywords Cognition · Glutamate · Impulsivity · Treatment · Pharmacology · Addiction

Abbreviations

CANTAB	Cambridge Neuropsychological Test Automated Battery
CGI	Clinical Global Impressions
G-SAS	Gambling Symptom Assessment Scale
HAM-A	Hamilton Anxiety Scale Rating
HAM-D	Hamilton Depression Scale Rating
IDED	Intra-dimensional/Extra-dimensional Set Shift task

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NMDA	N-methyl D-aspartate
PG	Pathological Gambling
PG-YBOCS	Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling
QoLI	Quality of Life Inventory
SCID	Structured Clinical Interview for DSM-IV
SDS	Sheehan Disability Scale
SST	Stop Signal Test

Introduction

Pathological gambling (PG), a significant public health problem characterized by persistent and recurrent maladaptive patterns of gambling, is associated with impaired functioning, reduced quality of life, and high rates of bankruptcy and divorce (Petry 2005; Grant et al. 2010). Past year adult prevalence rates for PG are estimated at 1% (Cunningham-Williams et al. 1998; Shaffer et al. 1999). Because untreated PG can impair functioning in multiple domains (Potenza et al. 2002), validated treatments are needed to optimize mental health care.

Currently, there is no Food and Drug Administration-approved pharmacological treatment for PG, despite almost a decade of intense research. Controlled clinical trials evaluating medication treatments for PG have demonstrated that opioid antagonists (Kim et al. 2001; Grant et al. 2006, 2008), as well as lithium (Hollander et al. 2005), show promise in reducing gambling urges, thoughts, and behaviors. Similarly, psychosocial interventions, particularly cognitive behavioral therapy, have become established treatments for PG but few individuals seek these treatments or can find trained therapists (Petry et al. 2006; Grant et al. 2009). Despite the promise from current treatments, they do not appear effective for all individuals with PG, and so additional treatment options are needed.

The repetitive deleterious behaviors characteristic of PG can be conceptualized as the result of an imbalance between two competing and relatively dissociable neurobiological mechanisms, namely those mediating urge and those mediating cognitive control. From a systems perspective, PG may be driven by an excess of activity in the mesocorticolimbic dopamine system and a lack of top-down cortical control governing response suppression and flexible responding. Previous pharmacological approaches for PG have targeted reduction in urges using opiate antagonists via modulation of mesolimbic dopamine (Kim et al. 2001; Grant et al. 2006, 2008) or using N-acetyl cysteine which restores extracellular glutamate concentration in the nucleus accumbens and thereby blocks reinstitution of compulsive behaviors and decreases cravings (Baker et al. 2003; Grant et al. 2007).

Memantine has the potential to reduce PG cravings via antagonism of the NMDA (N-methyl D-aspartate) receptors in the striatum (Krystal et al. 2003; Meisner et al. 2008; Ma et al. 2009). Additionally, and in contrast to the other potential treatments outlined above, memantine may also be capable of improving aspects of cognition by modulating glutamatergic neurotransmission in the prefrontal cortex (Van Wageningen et al. 2010). The effects of memantine on objective aspects of cognition have been explored in few studies, with mixed results (for discussion of healthy volunteer studies see Repantis et al. 2010). Memantine has shown to be effective in the treatment of Alzheimer's disease (e.g., see Tariot et al. 2004), which is associated with progressive cognitive decline spanning both mnemonic (temporal) and executive (frontal) domains.

Based on these reports of memantine's potential mechanism of action, we conducted a pilot study to examine the tolerability and efficacy of memantine in the treatment of PG. The rationale for the use of memantine was therefore twofold: first, glutamatergic dysfunction has been implicated in the pathophysiology of substance addictions, disorders with phenomenological and possible neurobiological links to PG, and clinical reports support the possible efficacy of glutamatergic modulators in the treatment of addictions (Krystal et al. 2003); and second, dysfunction of cortically-dependent cognitive domains is suggested by the symptoms of PG, and frontal lobe function has been found to be modulated by memantine in brain imaging work (van Wageningen et al. 2010). Cognition was assessed in this pilot study using the intra-dimensional/extra-dimensional (IDED) shift task and the stop signal task (SST) from the Cambridge Neuropsychological Test Automated Battery (CANTAB). The IDED task assesses aspects of learning and cognitive flexibility, which have been shown to be dependent on distributed fronto-striatal circuitry including the dorsolateral prefrontal cortices (see e.g., Owen et al. 1991; Hampshire and Owen, 2006). 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 (e.g., Aron et al. 2004; Hampshire et al. 2010). We focused on these tasks since the symptoms of PG suggest underlying problems with shifting behavior (shifting attention away to non-gambling activities) and impulsivity (inappropriate premature actions that result in deleterious long-term outcomes). We hypothesized that memantine treatment would be associated with improvements in cognitive flexibility and response inhibition in PG.

Method

Subjects

Men and women aged 18–75 with a primary diagnosis of PG based on criteria in the Diagnostic and Statistical Manual (DSM)-IV were recruited by newspaper advertisements. Subjects were recruited from April 2008 through February 2010.

Exclusion criteria included: (1) unstable medical illness or clinically significant abnormalities on physical examination, (2) history of seizures, (3) myocardial infarction within 6 months, (4) current pregnancy or lactation, or inadequate contraception in women of childbearing potential, (5) lifetime history of bipolar disorder type I or II, dementia, or any psychotic disorder, (6) current DSM-IV substance abuse or dependence, except nicotine dependence, (7) positive urine drug screen at screening, (8) initiation of psychotherapy or behavior therapy within 3 months prior to study baseline, and (9) previous treatment with memantine.

Subjects who were currently taking psychotropic medications were allowed into the study as long as the dose of medication had been stable for 3 months prior to study inclusion and there were no plans to modify the dose during the study duration. Similarly, subjects attending Gamblers Anonymous were allowed to participate if attendance had been ongoing for at least 6 months prior to study entry. Subjects who changed doses of medication or started therapy or Gamblers Anonymous, based on their self-report, were discontinued from the study.

The institutional review board for the University of Minnesota approved the study and the informed consent. One investigator discussed potential risks of the study, as well as alternative treatments, with subjects. After complete description of the study, subjects provided written informed consent. This study was carried out in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

Study design

The study consisted of 10 weeks of open-label memantine. All eligible study subjects were started on memantine 10 mg/day for 2 weeks. The dose was increased to 20 mg/day after 2 weeks and to 30 mg/day after 4 weeks unless remission of PG symptoms was attained at a lower dose (remission was defined as no gambling urges and no gambling behavior for the previous 2 weeks). Subjects were seen every 2 weeks during the study. All assessments were performed at each visit. Subjects were provided a minimal travel reimbursement (for gas and parking fees) of $25 per visit which was not paid until all visits were completed.

Screening assessments

Subjects were evaluated at entry into the study by the Structured Clinical Interview for Pathological Gambling, a reliable and valid diagnostic instrument for DSM-IV PG (Grant et al. 2004). Psychiatric comorbidity was assessed using the Structured Clinical Interview for DSM-IV (SCID; First et al. 1995) and valid and reliable SCID-compatible modules for impulse control disorders (Grant et al. 2005). Medical history, physical examination, and urine toxicology were obtained.

Efficacy and safety assessments

Subjects were seen every 2 weeks for the 10-week study period. The primary outcome measure was the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS; Pallanti et al. 2005). The PG-YBOCS is a reliable and valid, ten-item, clinician-administered scale that rates gambling symptoms within the last 7 days.

Secondary measures that were used at each study visit included:

Gambling Symptom Assessment Scale The Gambling Symptom Assessment Scale (G-SAS) is a 12-item, reliable and valid, self-rated scale assessing gambling urges, thoughts, and behaviors during the previous 7 days (Kim et al. 2009).

Clinical Global Impression-Improvement and Severity scales The Clinical Global Impression-Improvement and Severity scales (CGI) consists of two reliable and valid seven-item Likert scales used to assess severity and change in clinical symptoms. The improvement scale ranges from 1="very much improved" to 7="very much worse." Clinician-rated improvement scores were performed at each visit. The CGI severity scale was used at each visit and ranges from 1="not ill at all" to 7="among the most extremely ill" (Guy 1976).

Percentage of "responders" at each visit was a secondary outcome measure. Response was defined a priori as a 35% or greater reduction in PG-YBOCS total score at endpoint compared to baseline (a measure used in previous PG studies) (Hollander et al. 2005) and a score of 1 or 2 on the CGI Improvement Scale ("very much improved" or "much improved").

Sheehan Disability Scale The Sheehan Disability Scale (SDS) is a three-item, reliable, and valid scale that assesses

functioning in three areas of life: work, social or leisure activities, and home and family life (Sheehan 1983).

Hamilton Depression Rating Scale The Hamilton Depression Rating Scale (HAM-D) is a valid and reliable, 17-item, clinician-administered rating scale assessing depression severity (Hamilton 1960).

Hamilton Anxiety Rating Scale The Hamilton Anxiety Rating Scale (HAM-A) is a reliable and valid, clinician-administered, 14-item scale that provides an overall measure of global anxiety (Hamilton 1959).

A secondary measure used only at baseline and study endpoint was the *Quality of Life Inventory* (QoLI; Frisch et al. 1993). The QoLI is a 16-item self-administered rating scale that assesses life domains such as health, work, recreation, friendships, love relationships, home, self-esteem, and standard of living. The QoLI has demonstrated excellent reliability and validity in nationwide normative studies and in studies of other impulse control disorders (Grant and Kim 2005).

Safety assessments at each visit included evaluations of sitting blood pressure, heart rate, and weight. Adverse effects were documented. Use of concomitant medications was recorded. Urine toxicology and urine pregnancy tests were performed only at screening. Compliance was monitored by pill count.

Cognitive assessments

Subjects undertook paradigms from the CANTAB (Cambridge Cognition Limited 2006) quantifying aspects of impulsivity (relating to response inhibition) and cognitive flexibility. All assessments were performed by technicians blind to the subjects' diagnostic status at baseline although the same technicians assessed subjects pre- and post-treatment. Interpretation of the cognitive tasks was performed by a rater blind to group assignment and pre- and post-treatment status (i.e., gamblers at baseline, gamblers at endpoint, and healthy controls at baseline).

Intra-dimensional/extra-dimensional set shift task The IDED task includes aspects of rule learning and behavioral flexibility, and was derived from the Wisconsin Card Sort Test (Lezak et al. 2004). Through trial and error, and feedback, volunteers attempt to learn a rule about which one of the two stimuli is correct. After each choice, feedback is given ('correct' or 'incorrect'). Once learning criterion is obtained (six consecutive correct responses), the computer changes the rule, and the volunteer must then adapt their behavior appropriately. There are nine stages to the task, requiring different components of set acquisition, reversal, and flexibility. Key measures are the number of task stages successfully completed and the total number of errors made (corrected for stages not attempted).

Stop-signal test The stop-signal test is a well-validated task quantifying the ability to suppress impulsive responses (Logan et al. 1984; Aron et al. 2004). Subjects observe a series of directional arrows appearing one at a time on a computer screen, and make speeded motor responses depending on the direction of each arrow, with a button box (left or right). On a subset of trials, an auditory beep occurs (the 'stop signal') which indicates that the subject should try to inhibit their response for that particular trial. By varying the time between presentation of the arrow and the occurrence of the stop signal dynamically, this task provides a sensitive estimate of the time taken by the subject's brain to stop a prepotent response, referred to as the 'Stop-signal reaction time'. Other measures include median reaction time for go trials, and the number of directional errors made.

A between-group analysis compared PG subjects with age- and gender-matched healthy control subjects (n=26) who had no psychiatric histories based on the SCID. A within-group analysis compared PG subjects pre- and post-treatment on cognitive tasks to examine changes on neurocognitive measures during the course of memantine treatment. At the time of post-treatment assessment, all subjects had taken memantine prior to the test session. An additional between-group analysis compared post-treatment PG subjects to baseline healthy controls to examine whether PG subjects after treatment differed from control subjects on task performance.

Data analysis

In all efficacy analyses, only subjects who returned for one visit after starting medication were included (n=29). Primary analysis used a last observation carried forward approach. Variables that were collected at baseline and final visit were analyzed using a paired t test or the nonparametric Wilcoxon test. The nonparametric Cochran Q test was used to analyze the binary responder variable. The remaining variables were analyzed using a repeated measures general linear model (GLM) analysis with polynomial contrasts across the repeated visits.

Changes in cognitive performance between baseline and end of treatment were assessed in PG subjects using paired t tests. Performance of PG subjects at baseline and at study end point were compared separately to baseline data from healthy volunteers using unpaired t tests.

This being a pilot study, all tests of hypotheses used a significance level of 0.05.

Results

Thirty-two subjects with current DSM-IV PG signed the informed consent and were enrolled. Three subjects never returned for their first evaluation (all three subjects reported that they decided against participating in the study). Twenty-nine subjects (mean age=50.4±13 years [range 28–66]; 18 [62.1%] female) with current DSM-IV PG were included in the baseline and efficacy analyses.

Demographics and clinical characteristics of the sample are presented in Table 1. Twenty-three subjects (79.3%) reported slot machines, two (6.9%) reported Internet stocks or sports betting, two (6.9%) reported video poker, and two (6.9%) reported blackjack as their primary problematic gambling activity. Over the previous 12 months, subjects reported losing a mean of 56.9% of their gross annual income to gambling. The mean gambling losses per week were $743.45±$687.70.

Nineteen subjects (65.5%) met diagnostic criteria for at least one lifetime co-occurring axis I disorder: nicotine dependence (n=19; 65.5%) and major depressive disorder (n=15; 51.7%) were the most common (Table 1). Three subjects (10.3%) met criteria for past-year major depressive disorder but were currently asymptomatic. Twelve (41.4%) subjects met criteria for current nicotine dependence. The 12 subjects with nicotine dependence reported smoking a mean of 19.6±8.6 cigarettes per day at baseline (they reported smoking a mean of 17.1±8.6 at study endpoint; p=0.486). Nicotine craving was not assessed.

Eleven (37.9%) were currently taking stable doses of the following psychotropic medications for at least 1 year: bupropion (n=6; mean dose 250 mg/day), citalopram (n=3; mean dose 33.3 mg/day), trazodone (n=2; mean dose 125 mg/day), dextroamphetamine (n=2; mean dose 60 mg/day), escitalopram (n=1; 10 mg/day), sertraline (n=1; 200 mg/day), and paroxetine (n=1; 40 mg/day). Only one subject was receiving ongoing supportive therapy for relationship issues. No one was receiving any type of therapy for gambling. No subject was currently attending Gamblers Anonymous; however, 13 (44.8%) subjects reported having attended Gamblers Anonymous in the past.

Efficacy results

Of the 29 subjects who returned for at least one visit, 28 (96.6%) completed the 10-week open-label study. The subject who discontinued treatment reported being unable to keep the study schedule. The retention rate in this study was higher than the 60–70% retention rates generally reported in other open-label studies of PG (Black et al. 2008; Black 2004). Scores on the PG-YBOCS decreased from a mean of 21.8±4.3 at baseline to 8.9±7.2 (p<0.001) at the end of 10 weeks (Table 2). Eighteen (62.1%) subjects met criteria as treatment responders (≥35% decrease in PG-YBOCS total score plus a CGI Improvement score of 1 or 2) at the end of the study. The mean effective dose of memantine was 23.4±8.1 mg/day. Responders and non-responders did not differ significantly on baseline characteristics (including cognitive performance; all p>0.10). Responders and non-responders did not significantly differ in baseline rates of other psychotropic medication use (38.9% compared to 40.0%, respectively, chi-square= 0.003, df=1; p=0.954). No baseline gambling, psychiatric, or functional variable was significantly associated with the non-treatment responsive group.

All variables had a significant (improving) linear trend in the curve for mean scores over visits. Variables that were collected at all six time points had a significant quadratic component (curvature in the line connecting mean scores over visits) except for the G-SAS overall total which approached significance (p=0.059). An examination of the mean score by visits shows that there was a marked improvement from baseline to visit 2 followed by a more gradual linear improvement over subsequent visits (Table 2).

On cognitive tasks, PG subjects were compared to healthy controls at baseline (Table 3). At baseline, PG subjects showed significantly longer (impaired) stop-signal reaction times and more ID/ED total errors. Within-group analyses of PG subjects at baseline and study endpoint showed a significant improvement in ID/ED total errors. Improvement on ID/ED total errors was significantly associated with baseline G-SAS scores (Pearson r=0.385, p=0.043) and was correlated, on a trend level, with improvement on the G-SAS at study endpoint (Pearson r=0.338, p=0.078). Between group analysis of PG subjects at study endpoint and healthy control baseline data demonstrated no significant differences. The incidence and severity of adverse experiences were consistent with prior studies (Farlow et al. 2008), and no unexpected experiences were reported (Table 4). Most adverse experiences were of mild to moderate intensity, and all adverse events resolved without sequelae. Mean values in HAM-D and HAM-A scores remained at low levels throughout the study.

Discussion

This pilot study, the first to examine the efficacy of an NMDA receptor antagonist in the treatment of PG, found that PG symptoms improved significantly in a majority of subjects. Though preclinical data and studies conducted in patients with Alzheimer's disease suggest potential pro-cognitive effects of memantine (Tariot et al. 2004; Minkeviciene et al. 2008), the current study is the first to explore effects of memantine treatment on specific cognitive functions, assessed with

Table 1 Demographic and clinical characteristics of individuals with pathological gambling

	Subjects (n=29)
Age	
Mean (± SD) [range], years	50.4 (13) [28–66]
Female, *n* (%)	18 (62.1)
Race/ethnicity, *n* (%)	
Caucasian	23 (79.4)
African-American	1 (3.4)
Asian-American	2 (6.9)
Native-American	2 (6.9)
Other	1 (3.4)
Marital status, *n* (%)	
Single	14 (48.3)
Married	8 (27.6)
Widowed/separated/divorced	7 (24.1)
Education, *n* (%)	
High school grad or less	3 (10.3)
Some college	12 (41.4)
College grad or post-college	14 (48.3)
Unemployed, *n* (%)	4 (13.8)
Age at PG onset	
Mean (± SD), [range], years	38.7 (11.5) [20–62]
Primarily strategic gamblers, *n* (%)[a]	7 (24.1)
Previous treatment for gambling, *n* (%)	
Gamblers Anonymous	13 (44.8)
Individual outpatient therapy	11 (37.9)
Inpatient/residential	5 (17.2)
Group therapy	1 (3.4)
Percentage of gross income lost to gambling in the previous 12 months	
Mean % (± SD)	56.9 (59.2)
Amount of money lost to gambling each week	
Mean (± SD) [range], dollars	743.5 (687.7) [40–3000]
Time spent gambling each week	
Mean (± SD) [range], hours	10.4 (5.7) [3–40]
Committed illegal acts due to gambling, *n* (%)[b]	8 (27.6)
Currently taking medication with possible psychotropic effects, *n* (%)	11 (37.9)
Comorbid lifetime disorders, *n* (%)[c]	
Major depressive disorder	15 (51.7)
Any anxiety disorder	4 (13.8)
Any eating disorder	1 (3.4)
Alcohol abuse/dependence	4 (13.8)
Drug abuse/dependence (excluding nicotine)	3 (10.3)
Nicotine dependence	19 (65.5)
Attention deficit hyperactivity disorder	2 (6.9)
Any other impulse control disorder	4 (13.8)

[a] *Strategic gambling* for example, cards, dice, sports (compared to non-strategic which includes slots, pull tabs)

[b] Illegal activities includes acts even if not known by authorities (e.g., forging or writing bad checks, embezzlement, prostitution, etc.)

[c] Comorbid lifetime disorders did not include bipolar disorder or psychotic disorders as these were exclusion criteria

CANTAB. It was found that cognitive flexibility improved significantly with memantine treatment in PG, and that PG subjects were comparable on cognitive tasks to healthy controls at study endpoint. These findings suggest that pharmacological modulation of the glutamate system may reduce gambling in PG, and may do so by improving neurocognitive function related to cognitive flexibility. Because impaired performance on the ID/ED task has been linked with prefrontal cortical function (Tait et al. 2009), and because memantine appears to modulate activity in the

Table 2 Changes on primary and secondary measures across visits (n=29)

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Statistic	df	p value
PG-YBOCS total score	21.8 (4.3)	14.8 (8.3)	12.8 (8.3)	11.4 (6.4)	9.3 (7.7)	8.9 (7.1)	85.568a	1, 28	<0.001 L
							10.825a	1, 28	0.003 Q
PG-YBOCS urges/thought subscale score	10.1 (3.7)	7.5 (4.1)	6.0 (4.0)	5.1 (2.8)	4.6 (3.7)	4.6 (3.3)	42.776a	1, 28	<0.001 L
							11.986a	1, 28	0.002 Q
PG-YBOCS behavior subscale score	11.8 (1.6)	7.3 (5.0)	7.0 (5.2)	6.3 (4.3)	4.7 (4.6)	4.3 (4.4)	96.956a	1, 28	<0.001 L
							7.265a	1, 28	0.012 Q
Responder, n (%) (35% improvement from visit 1 PG-YBOCS total score and CGI Improvement score of 1 or 2)	n/a	7 (24.1)	11 (37.9)	15 (51.7)	17 (58.6)	18 (62.1)	22.486q	4	<0.001
Dollars lost per week	743 (688)	n/a	n/a	n/a	n/a	309 (600)	−3.849w	n/a	<0.001
Hours gambled per week	10.4 (5.7)	n/a	n/a	n/a	n/a	4.0 (6.0)	−4.159w	n/a	<0.001
G-SAS total score	30.6 (6.8)	25.1 (8.3)	23.3 (10.1)	19.6 (9.2)	17.4 (12.0)	16.6 (9.5)	41.440a	1, 28	<0.001 L
							3.870a	1, 28	0.059 Q
HAM-A	5.5 (4.1)	3.9 (3.2)	3.4 (3.0)	3.3 (3.2)	2.8 (3.0)	3.1 (2.9)	14.046a	1, 28	0.001 L
							9.232a	1, 28	0.005 Q
HAM-D	5.5 (4.3)	4.5 (3.7)	3.6 (3.4)	3.4 (3.3)	2.9 (3.2)	3.1 (2.8)	14.299a	1, 28	0.001 L
							5.889a	1, 28	0.022 Q
SDS total score	12.8 (7.3)	8.7 (7.4)	8.1 (7.9)	7.0 (7.1)	5.6 (7.5)	5.2 (5.9)	25.538a	1, 28	<0.001 L
							4.988a	1, 28	0.034 Q
CGI severity	4.7 (0.7)	3.8 (1.3)	3.5 (1.4)	3.1 (1.1)	2.8 (1.4)	2.6 (1.3)	61.829a	1, 28	<0.001 L
							4.430a	1, 28	0.044 Q
CGI-improvement	n/a	3.0 (1.1)	2.8 (1.2)	2.5 (1.1)	2.3 (1.2)	2.0 (1.1)	19.378a	1, 28	<0.001 L
							0.029a	1, 28	0.866 Q
Quality of life T score	35.8 (16.8)	n/a	n/a	n/a	n/a	42.5 (16.6)	2.965t	28	0.006

Last observation carried forward. All values shown as mean±SD, unless otherwise indicated

Logistic regressions were run for responders dependent variable

Statistic: t t test, a F statistic from GLM repeated measures, w Wilcoxon test, q Cochran's Q, P value, L linear component across visits, Q quadratic component across visits, *PG-YBOCS* Pathological Gambling Modification of the Yale Brown Obsessive Compulsive Scale, *CGI* Clinical Global Impression Improvement, *G-SAS* Gambling Symptom Assessment Scale, *SDS* Sheehan Disability Scale, *HAM-A* Hamilton Anxiety Rating Scale, *HAM-D* Hamilton Depression rating Scale, *NA* not applicable

prefrontal cortex (van Wageningen et al. 2010), memantine may target cognitive inflexibility that results in gambling behavior despite adverse consequences.

Although memantine may be a promising treatment for PG, prior pharmacological studies in PG have shown that particular treatments have not been effective for all individuals with PG (Grant and Potenza 2006). These prior results may reflect the heterogeneity of individuals with PG and how this heterogeneity may necessitate individually tailored treatment approaches (Grant and Potenza 2006). It is possible that individuals with PG and cognitive inflexibility may respond preferentially to memantine. While this notion remains speculative and requires additional studies to examine its appropriateness, one future direction for the treatment of PG may be to better define cognitive subtypes of PG to guide pharmacological treat-

Table 3 Performance on cognitive tasks in pathological gamblers and healthy controls

	Performance (mean±SD)			Comparisons					
	Pathological gamblers (PG) (n=29)		Controls (n=26)	PG B v E		PG B v C		PG E v C	
	Baseline (B)	Endpoint (E)		T	P	t	p	t	p
IDED Stages completed	8.61±0.79	8.71±0.71	8.88±0.43	−1.36	0.184	−1.59	0.118	−1.05	0.298
IDED total errors (adjusted)	24.5±18.79	19.79±18.72	14.96±14.18	2.20	0.037	2.09	0.041	1.06	0.294
SST directional errors	2.57±3.87	3.25±4.8	1.46±1.9	−0.86	0.395	1.32	0.192	1.77	0.082
SST median go reaction time	507.2±126.47	505.45±172.05	467.14±102.16	0.09	0.932	1.27	0.208	0.98	0.329
SST SSRT	181.06±45.98	167.9±46.96	145.07±42.62	1.07	0.293	2.98	0.004	1.87	0.068

At baseline, PG showed sig. impaired IDED (IDED total errors, adjusted) and impaired SSRT versus normative data

At endpoint, PG were no longer significantly impaired on these two measures (not at all for IDED; but there was a trend for SSRT)

IDED total errors significantly reduced over treatment in PG

ment selection. Future placebo-controlled studies may target examination of memantine based on groups specifically characterized by cognitive flexibility.

This study represents, to our knowledge, the first trial of a glutamatergic agent in PG that has been supported by objective cognitive measures. Nonetheless, there exist several important limitations. First, the study was open-label, and it is possible that patient and clinician bias may have influenced the results. There may have been positive responses not attributable to drug such as positive effects of regular therapist contact and/or subjects feeling obliged to meet the expectations of the research. In addition, placebo response rates in PG studies have been high (up to 72%; Blanco et al. 2002), and therefore these results could be due to the effect of a placebo. Interestingly however, the assessment of cognitive tasks was blinded and confirmed the positive open-label results. Control subjects were tested at baseline only and this could affect interpretation of post-treatment results in the patients. PG is a chronic disease that may require long-term therapy. By design, this study did not assess treatment effects beyond a 10-week treatment period. It is possible that a longer course of treatment could result in continued and even greater reductions in gambling symptoms. Alternatively, memantine's therapeutic effects in PG might not endure beyond 10 weeks. Third, we enrolled subjects seeking pharmacological treatment, not psychotherapy. Therefore, these results may not generalize to the larger population of people with PG. Fewer exclusionary criteria in this study (e.g., most current axis I disorders were not grounds for exclusion), however, suggest that this sample may generalize to a large population of individuals with PG. As subjects who were taking stable doses of psychotropic medications were enrolled, these medications might have affected treatment outcome. Given that there was no differential treatment response based on whether or not a subject was taking other psychotropic medications, the evidence suggests that positive outcome is not simply due to memantine augmenting another agent. With respect to the neurocognitive measures, the absence of a placebo group makes it difficult to distinguish the extent to which IDED improvement over the course of treatment reflects potential influences of medication, practice effects, or symptom improvement per se. To rule out categorically a mediating role for practice effects in IDED improvement with memantine, a follow-up study using a controlled design will be required. To the knowledge of the authors, there are, as of yet, no data examining non-treatment practice/repeat testing effects in PG with the cognitive measures examined here. It is possible that practicing these cognitive tasks in conjunction with taking memantine could have a synergistic therapeutic effect on PG outcomes.

This investigation suggests that memantine may be effective in the acute treatment of PG by improving cognitive flexibility. As effective treatments for PG emerge, it becomes increasingly important that physicians and mental health care providers screen for PG in

Table 4 Adverse events based upon corresponding dosage of memantine

Adverse event	10mg (n=29)	20mg (n=24)	30mg (n=16)
Light-headed/dizzy	2 (6.9)	4 (16.7)	2 (12.5)
Headache	3 (10.3)	0 (0)	0 (0)
Lethargic or tired	0 (0)	1 (4.2)	3 (18.8)
Decreased libido	0 (0)	1 (4.2)	1 (6.3)
Nausea	0 (0)	0 (0)	2 (12.5)

All numbers are N (%)

order to provide timely treatment. Given the open-label design of the study and the small number of subjects participating, however, the interpretation of the efficacy results of this study is limited. This study supports the future explication of pro-cognitive effects of memantine using controlled designs, in healthy volunteers and in clinical disorders associated with deficient cognitive flexibility.

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