

Sustained-release bupropion in the treatment of SSRI nonresponder pathologic gamblers: pilot study and review of the literature

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Background: Pathologic gambling (PG) is a prevalent and disabling impulse-control disorder. Recent studies have consistently demonstrated that PG patients respond well to treatment with selective serotonin reuptake inhibitors (SSRIs), mood stabilizers and opioid antagonists. These findings have supported the observation that PG is strongly associated with mood disorders, obsessive-compulsive spectrum disorders, panic disorder and addictive disorders. The aim of the study was to show the effectiveness of bupropion sustained release in PG. **Methods:** A total of 16 male PGs who had failed two previous trials of SSRI pharmacotherapy were enrolled in the study and were treated with bupropion sustained release for 12 weeks. A comprehensive psychiatric diagnostic evaluation was performed on all patients at baseline, and patients were screened for symptoms of gambling, depression and anxiety using the South Oaks Gambling Screen, the Hamilton Depression Rating Scale, the Hamilton Anxiety Rating Scale and the Clinical Global Impression-Improvement Scale. In addition, the patients completed self-report questionnaires concerning their demographic status. **Results:** Most patients responded well to bupropion treatment. A total of 12 out of 16 subjects completed the 12-week treatment program. Treatment response was determined by the level of gambling behavior reported by subjects at the 12-week visit. Full remission of gambling behavior was defined as the absence of gambling behavior for a period of 1 week prior to the follow-up visit. A total of nine out of the 12 completers reported full remission, and three completers had partial remission. **Conclusion:** Bupropion SR could be effective in the treatment of pathologic gamblers who are SSRI nonresponders.

Pathologic gambling (PG) is classified in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as a disorder of impulse control [1]. In the International Classification of Diseases of the World Health Organization [2], PG is coded under the heading of Habit and Impulse Disorders together with kleptomania, pyromania and trichotillomania. Impulse-control disorders are characterized by an overwhelming urge to perform a harmful act. PG is a chronic, progressive, male-dominated disorder, which has a prevalence of 1.0 to 3.4% among US adults [3] and the prevalence may be even higher among adolescents [4,5]. Emerging data in the field shows that PG is associated with a range of psychiatric comorbid diagnoses [6]. Hollander and colleagues [7] and McElroy and colleagues [8] describe a connection between the clinical features of PG and bipolar disorder. They describe characteristics common to both disorders such as impulsive risk-taking behavior, mood swings, poor judgement and grandiose thinking. Hollander and Wong suggested that impulsive disorders such as PG are associated

with strong compulsive and impulsive features and hence PG can be viewed as 'impulsive subtype' of the 'obsessive-compulsive (OC) spectrum' disorders [9]. According to this theory, a common unifying theme among the OC spectrum disorders is their selective responsiveness to treatment with SSRIs. PG has also been shown to overlap with the field of addictive disorders [10,11] and the opioid antagonist naltrexone has been shown to be effective in the treatment of PG [12].

Bupropion is an effective antidepressant, which has been used for the treatment of depressive disorders for more than two decades [13]. Bupropion acts *in vivo* as a dopamine (DA) and norepinephrine (NE) reuptake blocker [14] and therefore increases the extracellular levels of DA. Bupropion affects not only DA and NE, but also the nicotine, γ -aminobutyric acid (GABA) and glutamate receptors. Bupropion SR has been shown to be effective in the treatment of nicotine dependence and appears to decrease the sense of pleasure associated with smoking behavior as mediated by the dopaminergic system [15].

Keywords: addictive disorders, bupropion sustained release, impulsive behavior, pathologic gambling, selective serotonin reuptake inhibitors



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The authors believe that PG shares characteristics of both addictive behaviour and disorders of impulse control. We hypothesize that bupropion SR could decrease the cravings, urges and sense of pleasure associated with gambling and, in this way, could be effective in the treatment of PG.

Methods

Over the past 4 years, we have treated a group of over 200 PG patients. The patients were originally referred to us from all over Israel, either by their general physician or by their families. The study began at the Sheba Medical Center, which is a large tertiary care facility and was completed at the Rehovot Community Mental Health and Rehabilitation Clinic. For this pilot study, we recruited a sample of 23 male PG patients from our patient registry who met the following inclusion criteria:

- All patients had a diagnosis of PG according to DSM IV criteria and South Oaks Gambling Screen (SOGS) of 5 or more
- Patients were aged 18 to 65 years
- All 23 patients had failed two consecutive 8-week trials of treatment with SSRIs

In particular, patients had failed trials of fluvoxamine up to 200 mg/day and paroxetine up to 60 mg/day. SSRI treatment failure was defined as nonresponse after 8 weeks of treatment or inability to complete 8 weeks of treatment due to side effects. Exclusion criteria were:

- Comorbid axis I diagnosis of major depression, mania, schizophrenia or substance dependence
- Comorbid axis II diagnosis of borderline or antisocial personality disorder
- History of seizure disorder or unstable medical condition
- Current use of psychotropic medication or currently received bupropion

Patients who were occasional users of alcohol or drugs were allowed in the study, although patients who met criteria for substance dependence were excluded. Of the 23 patients who were eligible for the study and who met inclusion and exclusion criteria, 16 patients agreed to enroll in the study and receive 12 weeks of bupropion pharmacotherapy. At baseline visit, all study subjects underwent a comprehensive psychiatric diagnostic evaluation by two senior psychiatrists (Pinhas N Dannon and Katherine Lowengrub). The patients also completed

self-report questionnaires about their demographic status and signed an informed consent. The study was approved by local Hospital's Ethics Committee and the Ministry of Health.

In our cohort of 16 patients, bupropion SR was started at 150 mg/day for the first week and then increased to 300 mg/day in two divided doses. After 3 weeks of treatment, 14 out of 16 partial responders or nonresponders were increased to a total daily dose of 450 mg/day. Patients were monitored by the treating psychiatrists on a weekly basis for the first month of the study and then every 2 weeks for the duration of the study. The treating psychiatrists also monitored the patients' symptoms of alcohol and nicotine abuse at the time of the medication visits although we note that random urine drug screens were not performed to confirm sobriety.

One masked rater who is a senior psychiatrist, with significant experience in the field of PG, performed rating scales at baseline and at the 12-week end point. At the 12-week visit, patients were also asked to give a self-report on their level of gambling behavior. In addition, an interview with the family and/or referring source on the level of gambling behavior in the study subjects was performed at the 12-week visit.

Instruments

The authors administered the Hamilton Rating Scale for Anxiety [16], the Hamilton Depression Rating Scale [17] and the Clinical Global Impression-Improvement Scale [18] at baseline and at the 12-week follow-up visit. The SOGS [19] was administered at baseline. Baseline was defined as the day prior to starting bupropion pharmacotherapy.

Analysis

Statistical analysis was performed with t-test analysis. Levels of significance were set at 0.05, unless otherwise stated.

Results

A total of 13 out of 16 study subjects completed the 12-week trial. Two patients dropped out at week 2 of the study due to side effects of bupropion SR such as dizziness, vertigo and gastrointestinal disturbances, and one patient left the out-patient clinic without notice in order to receive treatment in a private practice. By week 12 of the study, nine out of 13 patients who completed the study reported full remission of gambling behavior over the last week of the study, and three out of 13 completers

reported an improvement in gambling behavior. Interviews with family members or the referring source confirmed the patient reports. Full remission of gambling behavior was defined as the absence of gambling behavior for a period of one week prior to the 12-week follow-up visit. Of the 16 study subjects who were enrolled in the trial, no serious adverse effects of bupropion SR (such as seizures) were seen.

The baseline scores of all 16 subjects as measured by the SOGS were consistent with PG (≥ 5). The mean Hamilton Depression Rating Scale 17-items score was 8.8 ± 6.3 at baseline, and at week 12 of treatment, the mean score was 6.8 ± 9.3 ($p = \text{ns}$). The Hamilton Rating Scale for Anxiety score was 11.9 ± 0.1 at baseline and, at the 12-week follow-up, the mean score was 11.2 ± 8.6 ($p = \text{ns}$). The above results of the Hamilton Depression Rating Scale and the Hamilton Rating Scale for Anxiety show that our cohort of patients were not depressed and did not suffer from pathologic anxiety at baseline or at the 12-week follow-up visit. The Clinical Global Impression (improvement) score was significantly better at the 12-week visit than the baseline visit ($t = 10.5$; $p < 0.001$).

The patients ranged in age from 27 to 69 years (38.2 ± 23.6). All of the completers, except one, were married. An analysis of social status of the completers demonstrated that three patients had a university degree; eight patients finished high school and one patient did not complete high school. Four of the gamblers were born in Israel, five in Eastern European countries and three in North Africa. All of the patients had a full-time job. Three out of 16 subjects met criteria for alcohol misuse and five out of 16 met criteria for nicotine abuse. The patients had various gambling debts ranging between US\$1800 and 200,000.

The mean age of onset (mean standard deviation) of pathologic gambling was 29.2 ± 17.5 years, ranging from 15 to 44, and most patients reported a gradually progressive course of the disorder with a gradual increase in the frequency and severity of gambling behavior.

Discussion

This is one of the first studies, to our knowledge, to examine the use of bupropion in the treatment of PGs who are nonresponders to SSRI pharmacotherapy. The results of our study suggest that bupropion SR is well tolerated and may be beneficial in reducing gambling behavior, for in our study sample, nine out of 13 completers

had a full response to treatment. We note that the improvement observed in the study subjects does not appear to be related to an antidepressant effect of bupropion, the HDRS scores were within normal limits at baseline and did not change significantly at the 12-week end point. Our results are consistent with Black's recent 8-week, open-label trial ($n = 10$) in which it was reported that seven out of ten PGs had a significant improvement with bupropion SR pharmacotherapy [20]. Similarly, Dannon and colleagues reported positive results of bupropion for PG in a small, open-label trial [21].

The pharmacologic approach to PG represents a field receiving growing interest in recent years. To date, a range of pharmacologic agents have been reported to be useful for the treatment of gambling behavior and related urges with the most convincing evidence coming from studies with SSRIs [22–24] followed by the mood stabilizers [25] and the opioid antagonist naltrexone [26]. A standard pharmacological approach for PG; however, is far from being established, and in the case of SSRIs, a recent double-blind study failed to show efficacy of SSRI treatment [27]. It has been proposed that PG is a heterogeneous disorder which overlaps with both OC spectrum disorders [28] and addictive disorders [29] and some authors have hypothesized that there are specific subtypes of pathologic gamblers with specific patterns of treatment response within this population [30]. We propose that bupropion may represent a pharmacological option for SSRI nonresponders because bupropion does not appear to work via serotonergic pathways.

Several lines of evidence suggest that bupropion SR may have a role in the treatment of PG. Firstly, bupropion SR selectively inhibits the reuptake of DA and NA, which, in turn, stimulate acetylcholine, hydroxytryptamine and GABA receptors as well as endorphins [31]. All of these psychoactive systems may play a role in the pattern of urges, cravings and sense of enjoyment seen in pathologic gambling behavior and disorders of chemical addiction. Clinical studies have shown that naltrexone reduces the craving for alcohol and promotes abstinence [32,33] and like naltrexone, bupropion has been tested in the field of chemical addiction. Bupropion has been shown to reduce nicotine withdrawal symptoms and the urge to smoke and has US Food and Drug Administration (FDA) approval for the treatment of nicotine dependence [34]. In a small single-blind trial, bupropion was also shown to

be helpful in the treatment of comorbid cocaine abuse and attention-deficit/hyperactivity disorder (ADHD) [35]. Two case reports have described the successful use of bupropion in amphetamine addiction [36,37], and in both cases, amphetamine withdrawal symptoms and amphetamine cravings were significantly reduced. Whereas naltrexone has already been investigated for the treatment of urges and cravings associated with PG [38], bupropion, which has a more favorable side effect profile may represent a useful alternative for pathologic gamblers.

Bupropion not only acts at the level of the mesolimbic pathway, but is also structurally related to amphetamine and the sympathomimetic diethylpropion [39]. The known comorbidity between PG and ADHD as well as the association between PG and impulsive behavior [40] have led investigators to postulate that bupropion may represent a logical treatment option in PG.

Surprisingly, in our study, no significant differences were seen in smoking habits before and after treatment with bupropion SR. Perhaps the comorbid diagnosis of PG made the symptoms of nicotine dependence more resistant to treatment. Alternatively, our sample size may have been too small to detect meaningful effects of bupropion SR on smoking behavior. Three out of twelve patients who completed the trial also had a diagnosis of comorbid alcohol misuse. These three patients showed a clinically significant decrease in both alcohol consumption and symptoms of alcohol abuse

while treated with bupropion SR. Although we cannot draw firm conclusions from our small pilot study, we suggest that bupropion may, like SSRIs, be useful in the treatment of comorbid PG and alcohol dependence. Therefore, pharmacologic treatment, which targets both the PG and the comorbid alcohol abuse, would be of great interest.

The primary limitations in this pilot study are the open-label design and the small sample size. In addition, our results may be influenced by selection bias, as our patients were selected from an ambulatory setting and patients with comorbid substance dependence and personality disorders were excluded from the study. Since these diagnoses are commonly comorbid with PG, the results of our study may not be generalizable to patients seen in actual clinical practice. Despite these limitations; however, our pilot study suggests that bupropion SR may be an effective treatment for PG. Our results are strengthened by the fact that our patient sample was selected from a group of patients who were considered to be nonresponders to two SSRI trials. Further studies in a larger, more varied patient sample are clearly warranted in order to evaluate the effectiveness of bupropion SR in pathologic gambling and, by extension, in other impulsive-addictive spectrum disorders.

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