Acamprosate and baclofen were not effective in the treatment of pathological gambling: preliminary blind rater comparison study

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INTRODUCTION

Pathological gambling (PG) is classified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, as an impulse control disorder (American Psychiatric Association, 2000). In the International Classification of Diseases of the World Health Organization, PG is considered a habit and impulse disorder, alongside kleptomania; trichotillomania, and pyromania, all of which are characterized by an overwhelming urge to perform a harmful act (World Health Organization, 1992). PG is a chronic, progressive, male-dominant disorder, causing great personal and social consequences such as suicide attempts, job loss, marital and family problems, legal problems, and criminal behaviors (Dannon et al., 2006; Iancu et al., 2008).

To date, a range of psychopharmacological options are available for the treatment of PG, including selective serotonin reuptake inhibitors (SSRI), opioid receptor antagonists, anti-addiction drugs, and mood stabilizers.

Multiple randomized, double-blind as well as open-label short-term (8, 12, or 16-week) trials have assessed pharmacotherapy for the acute treatment of PG. As a group, these trials show an overall mixed success with several double-blind studies failing to show short-term efficacy. To date, there have been four double-blind trials of SSRI agents for the treatment of PG. While two studies showed short-term efficacy (Hollander et al., 2000; Kim et al., 2002), separate studies by Blanco et al. (2002) and Grant et al. (2003) found no significant statistical superiority of the SSRI agent when compared to a placebo. Preliminary studies have examined the use of the mood stabilizers, topiramate (Dannon et al., 2005a), and anti-addiction drug, bupropion (Black, 2004; Dannon et al., 2005b,c), for the short-term treatment of PG with most studies showing a beneficial effect. In addition, the anti-addiction, opioid antagonist naltrexone, has been shown to be beneficial in treating the cravings and urges associated with PG (Kim and Grant, 2001; Kim et al., 2001).

It is well accepted in the clinical literature of PG that there are several important limitations of existing short-term medication trials: (1) variable rates of placebo response have been demonstrated in the short-term studies, raising the question of whether improvement seen in treatment groups may be related to non-medication mechanisms of action; (2) PG typically has a chronic course, and therefore acute remission of symptoms may not lead to a clinically significant improvement in functioning if the remission is not sustained; and (3) in all short-term studies published to date, remission of gambling symptoms was judged, at least in part, according to patients’ self-reports of gambling behavior which may be biased (Dannon et al., 2007).

The opioid system controls the processing of reward, pleasure, and pain, alongside gambling-related urges. Data suggests that opioid receptor antagonists mediate their therapeutic action in the treatment of addictive disorders through the modulation of GABA neuronal input to dopamine neurons in the mesolimbic pathway (Kim and Grant, 2001; Kim et al., 2001). GABA represents the main inhibitory neurotransmitter in the brain. High levels of GABA receptor expression in the limbic system indicate a role in regulating emotional behavior (Addolorato et al., 2009). The assumption is being that the GABA receptors may play a role...
in the pattern of urges, craving, and sense of enjoyment seen in PG behavior (Addolorato et al., 2009).

The brain’s reward circuit, located in the nucleus accumbens, ensures reinforcement of behaviors associated with species survival and procreation. The opioid system is involved in the process of reward, pleasure, pain, and gambling-related urges. It has been suggested that opioid receptor antagonists mediate their therapeutic action in the treatment of addictive disorders through the modulation of GABA neuronal input to dopamine neurons in the mesolimbic pathway (Addolorato et al., 2009). The above data had us to believe that GABA directed addiction drugs, such as baclofen and acamprosate, might be efficient in the treatment of PG.

Alcohol has been proven to affect GABA neurotransmitters in the brain, and anti-addiction drugs have been shown to be efficient in decreasing the consumption and craving of alcohol. Acamprosate is believed to increase the effect on the inhibitory neurotransmitter GABA and to decrease excitatory glutamate activity at NMDA receptors (Addolorato et al., 2009). Baclofen is known to suppress alcohol-stimulated dopamine release in the shell of the nucleus accumbens of rats (Addolorato et al., 2009), and its administration has been shown to promote alcohol abstinence and reduce alcohol craving and intake; it has also been shown to reduce anxiety (Addolorato et al., 2006).

Previous experience with anti-addiction medications, such as bupropion and naltrexone, has been shown to be the most effective for the treatment of PG (Kim and Grant, 2001; Kim et al., 2001; Black, 2004; Dannon et al., 2005b,c). Based on the effectiveness of anti-addiction drugs, we examined the efficacy of two other medications, baclofen and acamprosate. The difference between the two groups is the system on which the drug affects; while bupropion and naltrexone affect the reward system and the neuro-transmitter dopamine, the baclofen, and acamprosate could affect the GABA system.

In our study, we tested the efficacy of two addiction drugs, acamprosate and baclofen, which stimulate the GABA receptors, and have been proven to be effective in the treatment of alcohol abuse (Addolorato et al., 2009).

1 Acamprosate
Acamprosate (calcium acetylhomotaurinate) is a simple derivative of the essential taurine amino acid which displays a structural resemblance to gamma-amino butyric acid (GABA; American Psychiatric Association, 2000). It was approved by the US FDA in 2004 for treatment of alcoholic patients to decrease alcohol craving after alcohol detoxification. Acamprosate seems to bind specifically to GABA_B receptors (Boothby and Doering, 2005). It enhances GABA reception and the transmission of the GABAergic system, raises the continuous alcohol abstinence rate and doubles the days of cumulative abstinence from alcohol (Boothby and Doering, 2005). Acamprosate is not a sedative; it does not possess addictive properties or provide reinforcing effects.

2 Baclofen
Baclofen [beta-(4-chlorophenyl)-GABA] is a GABA_B receptor agonist that has been found to suppress both acquisition of alcohol drinking behaviors in rats and daily alcohol intake in alcohol experienced rats. It also suppresses alcohol-stimulated dopamine released in the shell of the nucleus accumbens of rats (Addolorato et al., 2009).

In alcohol dependant subjects, baclofen administration promotes alcohol abstinence, induces the remission of withdrawal symptoms, and reduces alcohol craving and alcohol intake (Addolorato et al., 2006).

MATERIALS AND METHODS

STUDY SUBJECTS

Patients were referred to our clinic, from ambulatory services throughout Israel, on account of our gambling disorder expertise. All study patients signed an informed consent form after possible side effects of the study medications were explained to them. Current study was approved by local IRB committee to publish the results of clinical trial. Patients also gave consent for family members to be interviewed at the monthly follow-up visits. Inclusion criteria included: PG diagnosis according to DSM-IV-TR criteria and South Oaks gambling scale (SOGS) score of more than 5. Exclusion criteria included: co-morbidity with axis one psychiatric disorders, neurological disorders, alcohol and substance abuse, and treatment with any psychiatric medication in the month before to the screening interview.

All patients underwent a comprehensive psychiatric diagnostic evaluation and completed a series of semi-structured interviews performed by a senior psychiatrist (PND).

Study subjects were evaluated on a monthly basis throughout the duration of the study in order to assess measures of sustained improvement (i.e., abstinence) and relapse. In this study, abstinence was strictly defined as no gambling behavior (including any form of gambling) during the month preceding the follow-up visit. Relapse was defined as any gambling behavior during the month preceding the follow-up visit.

Instruments

We administered the Hamilton rating scale for anxiety (HARS; Hamilton, 1959), the Hamilton depression rating scale (HDRS; Hamilton, 1959, 1960), visual analog scale (VAS; Guy, 1976), and the South Oaks gambling screen (SOGS; Leisure and Blume, 1987) at baseline. HARS, HDRS, VAS were administered at every monthly follow-up visit. The patients’ self-reports regarding amount of time spent gambling was assessed at each follow-up visit although a structured interview was not performed. Collateral information regarding gambling behavior was collected from family members at the monthly follow-up visits. All scales were administered by the rater (TL) who was blind to drug treatment.

MEDICATION

Patients were randomly assigned to treatment with baclofen or acamprosate. Treatment with baclofen was conducted as follows: 10 mg per day for the first 4 days, than 20 mg for the next 4 days, and than 30 mg with stable condition up to 3 weeks. Average dosage of baclofen was 30 mg per day (SD + 7.5). Some patients were treated with up to 50 mg per day.

Treatment with acamprosate was conducted as follows: 333 mg for the first 4 days than 666 mg for a week and afterward 999 mg per day. Average dosage of acamprosate was 666 mg (SD + 174).
Table 1 | Demographic characteristics of the patients.

|                        | Baclofen (N = 9) | Acamprosate (N = 8) | P values |
|------------------------|------------------|---------------------|----------|
| Age                    | 29.7 ± 13.5      | 30.4 ± 11.9         | NS       |
| Ethnicity %            |                  |                     |          |
| North African decent   | 46               | 50%                 | NS       |
| Eastern European decent| 30%              | 24%                 | NS       |
| Israeli born           | 24%              | 26%                 | NS       |
| Education %            |                  |                     |          |
| 12th grade             | 40%              | 40%                 | NS       |
| High School diploma    | 36%              | 40%                 | NS       |
| University             | 24%              | 20%                 | NS       |
| Employment %           |                  |                     |          |
| Unemployed             | 18%              | 16%                 | NS       |
| Full/part time         | 82%              | 84%                 | NS       |
| Marital status %       |                  |                     |          |
| Married                | 70%              | 66%                 | NS       |
| Widowed–divorced–separated | 18%          | 20%                 | NS       |
| Never married          | 12%              | 14%                 | NS       |

Table 2 | Statistical comparison of HDRS, HARS, and VAS scores of patients treated with acamprosate and baclofen.

|                                | Visual analog scale | Hamilton depression rating scale | Hamilton anxiety rating scale |
|--------------------------------|---------------------|---------------------------------|------------------------------|
| Unpaired T-TEST at baseline    | P > 0.74            | P > 0.86                        | P > 0.78                     |
| Unpaired T-TEST after 1 month  | P > 0.73            | P > 0.9                         | P > 0.1                      |
| of treatment completion        |                     |                                 |                              |
| Unpaired T-TEST at the time of | P > 0.3             | P > 0.9                         | P > 0.97                     |
| relapse                        |                     |                                 |                              |

HDRS, Hamilton depression rating scale; HARS, Hamilton anxiety rating scale; VAS, visual analog scale.
Table 3 | Average scores and SD of HDRS, HARS, and VAS.

| Table 3 | Average scores and SD of HDRS, HARS, and VAS. |
|---------|------------------------------------------------|
|         | Baseline | After 1 month | At the time of relapse |
| HDRS    | 10.1 ± 2 | 10.6 ± 1      | 10.6 ± 1.5             |
| HARS    | 11.25 ± 166905 | 11.75 ± 0.707 | 11.9 ± 0.64           |
| VAS     | 52.5 ± 11.6 | 51.8 ± 10.3   | 49.3 ± 6.2            |
|         | Baclofen   | Acamprosat    | Baseline | After 1 month | At the time of relapse |
|         |           |              | 10.3 ± 1.5 | 10.7 ± 1.7 | 10.7 ± 1.2 |
|         |           |              | 11 ± 1.732 | 10.9 ± 1.21 | 11.9 ± 1.07 |
|         |           |              | 54.3 ± 8.4 | 53.6 ± 8.5 | 52.8 ± 6.3 |

HDRS, Hamilton depression rating scale; HARS, Hamilton anxiety rating scale; VAS, visual analog scale.

The importance of pharmacological preliminary studies such as our study ensues from the fact that no established pharmacotherapy exists. Potentially effective directions for future pharmacotherapy need to be explored on the basis of preliminary studies, or alternatively, as in this case, be renounced.

LIMITATIONS
The small sample size of this study limits the power of the study. Another limitation is patients were not blind to pharmacotherapy.

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