Journal Information
Journal ID (publisher-id): jgi
ISSN: 1910-7595
Publisher: Centre for Addiction and Mental Health

Article Information

Received Day: 11 Month: November Year: 2003
Publication date: February 2004
Publisher Id: jgi.2004.10.10
DOI: 10.4309/jgi.2004.10.10

The role of medication in the treatment of pathological gambling: Bridging the gap between research and practice

Richard J. Rosenthal

Affiliation: *UCLA Gambling Studies Program, Los Angeles, California, U.S.A. E-mail*: *rrosenth@ucla.edu*

[The article prints out to about 53 pages.]

Acknowledgements:*The author would like to thank Timothy Fong, MD, David Gorelick, MD, Loreen Rugle, PhD, Hermano Tavares, MD and Jeffrey Wilkins, MD for their helpful comments*.

Correspondence: **For correspondence***Richard J. Rosenthal, MD, 435 N. Roxbury Drive, Beverly Hills, CA 90210, U.S.A. Tel: (310) 278-3746, Fax: (310) 278-1958. E-mail*: *rrosenth@ucla.edu*
Richard J. Rosenthal, MD, has been treating pathological gamblers for almost 25 years. He co-authored the DSM-IV diagnostic criteria, was co-investigator on the first genetic study of gamblers and has published articles and book chapters on the phenomenology of pathological gambling, its course, complications and treatment. Dr. Rosenthal was a member of the National Academy of Science's Committee on the Social and Economic Impact of Pathological Gambling. He founded the California Council on Problem Gambling and has been actively involved in the National Council. In addition to his private practice and teaching duties, he is co-director of the UCLA Gambling Studies Program.

Abstract

After reviewing the literature on the pharmacotherapy of pathological gambling, the author discusses treatment strategies and areas for future research. The clearest indication for medicating the pathological gambler is for the treatment of comorbid disorders, primarily depression, bipolar disorder, and attention deficit hyperactivity disorder. However, there are difficulties in diagnosing the dually disordered gambler. Other current pharmacological approaches involve the use of medication

to treat specific symptoms, traits, or symptom clusters; to make negative affects more tolerable; and to reduce cravings. Future approaches will be directed at subgroups of gamblers. This may include genetic profiling, paired with recognition of neurotransmitter deficits, and the identification of clinical syndromes and subtypes. The author also discusses the kindling hypothesis as it may pertain to pathological gambling. The presence of kindling would make a strong case for earlier and more aggressive use of medication and for long-term maintenance to prevent relapse.

Introduction

Medication should be thought of as an adjunct to the treatment of pathological gambling. Most gamblers can be treated successfully without it. Even when one does prescribe medication, it is still necessary to help the patient identify and express feelings, confront difficult situations, develop social skills, and deal with relationship problems. In fact, medication is given in the context of a relationship.

It is in the therapeutic relationship that we observe and try to solve problems in compliance. Less than 40% of patients with physical illnesses follow the doctor's instructions for dose and frequency of their medications (Buckalew & Buckalew, 1995; review by O'Brien & McLellan, 1996). One-third of the general population does not get prescriptions filled, and over 40% will use someone else's medication (Buckalew & Buckalew, 1995). Full compliance occurs only 25% of the time. Compliance is an even more serious problem with pathological gamblers because they are often ambivalent about giving up gambling or altering lifelong patterns of coping, no matter how ineffective these strategies may have been. What these gamblers often express is the feeling that something is being taken away from them. Problems with trust exist for both therapist and patient.

Given such issues, what then is to be gained by attempting to medicate pathological gamblers? First of all, there are a number of studies that point toward the importance of biological factors in gambling addiction. Kruedelbach and Rugle (1994) found gamblers to be more impulsive than cocaine addicts or alcoholics, and also found that, at least for a subgroup of pathological gamblers, high impulsivity preceded the history of gambling problems. Studies of biological markers have suggested deficits in the serotonergic (Moreno, Saiz-Ruiz & Lopez-Ibor, 1991; Carrasco, Saiz-Ruiz, Hollander, Cesar & Lopez-Ibor, 1994; Blanco, Orensanz-Munoz, Blanco-Jerez & Saiz-Ruiz, 1996; DeCaria, Begaz & Hollander, 1998a), dopaminergic (Bergh, Eklund, Sodersten, Nordin, 1997), and noradrenergic (DeCaria et al., 1998a) systems. A genetic predisposition is suggested by family histories of problem gambling (Gambino, Fitzgerald, Shaffer, Renner & Courtnage, 1993; Winters, Stinchfield & Fulkerson, 1993; Winters,

Bengston, Dorr & Stinchfield, 1998), twin studies (Eisen et al., 1998; Slutske et al., 2000), and genetic research (Comings et al., 1996; Ibanez, Perez de Castro, Fernandez-Piqueras & Saiz-Ruiz, 2000; Comings et al., 2001). EEG (Goldstein, Manowitz, Nora, Swartzburg & Carlton, 1985) and neuroimaging studies utilizing PET scans and MRIs (Goyer, Semple, Rugle & McCormick, 1999; Potenza, 2001) show significant differences between pathological gamblers and normal controls. Potenza found that the gambling urges of the problem gambler activate the same regions of the brain (e.g. the anterior cingulate) as the cocaine cravings of people with chemical dependencies.

For the clinician, practical considerations argue for using medication. Medication can help to achieve abstinence and can help provide the much-needed structure and support necessary to maintain some patients in treatment. The continuation of gambling, with its potential for large, sudden financial losses, illegal activities that lead to incarceration, attempted suicide, and other serious consequences, can disrupt or threaten treatment. One cannot treat a patient who fails to show up. Even when the gambler is physically present, if still actively gambling he or she may be emotionally unavailable, dissociated, or cognitively impaired. We tend to think of medication more for the difficult-to-treat end of the spectrum, those patients who are multi-impulsive, who have multiple addictive and other comorbid disorders, who have severe and intractable cravings, and who act out or are noncompliant. These patients may make up a relatively small percentage of our treatment population, but they are the ones we spend the most time thinking about.

There are also economic considerations that argue for using medication, including pressures from managed care, reduced or nonexistent insurance coverage, and the already overburdened finances of most compulsive gamblers. While we speak of a continuum of care for addictive disorders, therapists treating gamblers are hard pressed to make do with what is available. For example, in many parts of the country Gamblers Anonymous (GA) may meet only weekly or not at all, and may not conform to patients' needs with regard to gender, age, ethnicity, or even language. Medication, again, helps to provide the structure and support needed for abstinence and recovery.

This paper will try to accomplish two things: first, to review the published research on the pharmacotherapy of pathological gambling and, second, to explore current and potential clinical approaches. Clinicians will always have to make choices based on what they are trying to accomplish. When choosing to medicate a pathological gambler, clinicians must consider what they are medicating, and in which pathological gamblers will a given medication be effective?

Review of the pharmacotherapy literature

Research on the pharmacotherapy of pathological gambling is in its infancy, with funding for clinical trials having only recently become available. The studies published to date (see Table 1)

(Click here to view the table: a new browser window will open.)

have utilized three classes of medications: serotonin reuptake inhibitors (SRIs), mood stabilizers and opioid antagonists. In this and the following sections, we will highlight promising areas of investigation and discuss gaps in the literature.

Serotonin reuptake inhibitors

Hollander, Frenkel, DeCaria, Trungold and Stein (1992) described the treatment of a female gambler with the partial serotonin reuptake inhibitor clomipramine (Anafranil). This medication was the first to receive FDA approval for the treatment of obsessive-compulsive disorder, and Hollander selected it for the first controlled study of pathological gambling because he thought that the two disorders were related. He and his colleagues conducted a double-blind, placebo-controlled study, 10 weeks to each phase. The patient was minimally improved on the placebo, then became abstinent on the medication and did not gamble for the duration of the trial. Except for a relapse at week 17, she remained abstinent on open maintenance for an additional seven months. Significant in her personality were some compulsive features, including perfectionism and hoarding. She also had a history of social phobia, another disorder that responds well to serotonergic drugs. Also noted was that this bingo, cards, and slot machine player had a prior history of a one-and-a-half-year abstinence with Gamblers Anonymous. However, when she entered the study she had been gambling consistently two to three times per week during the previous six and a half years.

Hollander et al. (1998) then conducted a single-blind placebo lead-in (eight weeks each phase) fluvoxamine (Luvox) study. Of 16 pathological gamblers, six dropped out during the placebo phase. Seven of the 10 who remained responded favorably, as measured by the clinician-rated Clinical Global Impression (CGI) scale and by the Yale-Brown Obsessive Compulsive Scale modified by the authors for pathological gambling (PG-YBOCS). Reliability and validity of the PG-YBOCS have been presented (DeCaria et al., 1998b) but are as yet unpublished. In addition to these positive measures of improvement, all seven responders described a decrease in cravings and the achievement of abstinence. Of the three fluvoxamine nonresponders, two had comorbid cyclothymia. Since fluvoxamine and the other SSRIs (selective serotonin reuptake inhibitors) can “switch” depressed patients into a manic phase or bring out an underlying bipolar disorder, there was concern about the medication exacerbating their cyclothymia, particularly at the higher dose (250 mg/day) administered to the nonresponders. The authors recommended that in future studies in which pathological gamblers are to be given SSRIs, subjects with

bipolar disorder (types I and II) should be excluded.

Following up on the promising data from their pilot study, Hollander et al. (2000) designed the first randomized double-blind placebo-controlled medication study on pathological gambling. Gamblers with substance abuse or bipolar disorder (type I or II) were excluded. Each subject received eight weeks of fluvoxamine and eight weeks of placebo, administered according to a cross-over design. Of the 15 pathological gamblers who began the study, 10 subjects (all males) qualified as minimum treatment completers by remaining in the study for at least 12 weeks. Dosage began with 50 mg of fluvoxamine, and was increased weekly to a maximum of 250 mg/day and a minimum of 100 mg/day based on therapeutic response and tolerance. There was a significant placebo response early in the study, so that fluvoxamine and placebo were both effective in phase I. The response to the placebo disappeared during the second phase, while the fluvoxamine response was sustained. Though there was only a trend towards significance on the PG-YBOCS, scores on the CGI scale were much improved or very much improved in 67% of the fluvoxamine group in phase II, as compared to just 25% of those on placebo. It should be noted that this was a very small sample. The number of fluvoxamine responders in phase II was four.

The authors concluded that fluvoxamine is well tolerated and may be effective in the treatment of pathological gambling. However, they point out the limitations of their research, specifically mentioning small sample size, short duration of treatment, and the homogeneity of their group of subjects with regard to gender, ethnicity, gambling preference, and absence of comorbidity. They acknowledge that their findings may not be applicable to the noncompliant, difficult-to-treat gambler. And, finally, they caution that the long-term effectiveness of fluvoxamine still needs to be evaluated.

Zimmerman, Breen and Posternak (2002) conducted an open-label study of citalopram (Celexa). Fifteen pathological gamblers were given the medication for up to 12 weeks. Most showed clinical improvement within the first two weeks; gains were maintained for the nine who completed. Since there were no controls, it is difficult to say this was not a placebo effect. It should be noted that patients in individual or group psychotherapy were not excluded as long as there was no change in the type or frequency of their therapy during the course of the study. Citalopram was begun at 10 mg/day, then increased to 60 mg depending on response and side effects.

As compared to Hollander's two studies, in which most of the subjects were early onset gamblers (average duration of problem gambling 20 years) engaged in the more traditional games (primarily horse racing or sports betting), all of Zimmerman's subjects were machine gamblers (n=13) or played lottery scratch-off tickets (n=2). Two-thirds had been problem gamblers for less than five years. In

order to more closely approximate a treatment population, Zimmerman did not exclude subjects with current depression, anxiety, eating disorders, or other impulse disorders. Therefore, eight of 15 subjects (53.3%) were diagnosed with major depressive disorder at baseline. The most common nondepressive comorbid disorder was panic disorder (20%, n=3). These comorbid disorders would be expected to respond to citalopram.

The authors reported that, in addition to decreases in days gambling and amount of money lost, there was a significant decrease in subjects' level of depression. To see whether improvement in gambling was due to the effect on comorbid depression, they compared those with major depressive disorder (n=8) and those without it (n=7) and found a similar response in both groups. However, it is possible that even those who did not have a major depressive disorder met criteria for subsyndromal depression or dysthymia. Unfortunately, the typical instruments for rating depressive symptoms are not well suited for evaluating more mildly depressed patients.

Blanco, Petkova, Ibanez and Saiz-Ruiz (2002) attempted to replicate Hollander's findings while addressing the question of efficacy over a longer time period. Thirty-two pathological gamblers were treated for six months in a double-blind, placebo-controlled study using the same dosage of fluvoxamine as Hollander's group. Outcome measures included reductions in money and time spent gambling per week. Subjects were allowed to use a benzodiazepine, clorazepate, for anxiety or insomnia, and the antiemetic domperidone for nausea. All patients were encouraged to attend self-help or therapy groups focused on pathological gambling.

The study failed to confirm Hollander's results. For the overall sample, fluvoxamine was not statistically different from placebo. However, it was superior to the placebo for a subgroup of males and younger patients. Two major problems were encountered by the research team. The first of these was a high placebo response that persisted well into the study. Even when they used abstinence as their measure of success, there was a 54% placebo response at the end of four months. A second problem was the high dropout rate among the fluvoxamine group. Of the 15 subjects who began on the medication, barely half were still enrolled by the midpoint of the study (12 weeks) and only three of the 15 lasted until the end of the trial. Reasons for noncompletion were lack of compliance (7), side effects of medication (3), or unknown (2). The authors noted that some of the patients who were dropped for noncompliance were actually experiencing clinical improvement. It is not clear what the compliance issues were. Similarly, there are difficulties knowing how to interpret the overall findings. Blanco used different outcome criteria from Hollander's group, and the high dropout rate makes interpretation of results problematic. The unexpectedly high placebo response may be due to subjects'

participation in gambling-related self-help and therapy groups. The authors acknowledge a lack of data on this.

Paroxetine (Paxil) was the subject of a double-blind, placebo-controlled study by Kim, Grant, Adson, Shin and Zaninelli (2002). Pathological gamblers who did not have a co-morbid Axis I disorder (as measured by the SCID-I) and were not in psychotherapy or attending GA were enrolled in a one-week placebo run-in phase followed by eight weeks' treatment with paroxetine. The number of women in the study (n=30) was double that of men (n=15), but severity of gambling symptoms was similar for both genders. Twenty-one of the 23 gamblers in the paroxetine group (91.3%) played slot machines. The second most common form of gambling was bingo (26.1%). Of the 45 subjects who were randomly assigned, only four failed to complete all study visits. Two from the paroxetine group missed single visits, and one from each group discontinued because of side effects. Dosages were increased in 10 mg weekly increments from 20 mg/day at the start of the study to a maximum of 60 mg/day. The medication was extremely well tolerated.

Statistically significant improvement on the CGI and on a 12-item instrument developed by the authors, the Gambling Symptom Assessment Scale (G-SAS), was found for weeks six through eight. As measured by the CGI, 47.8% of the paroxetine group was very much improved and 13% much improved by study endpoint, compared with just 4.5% and 18.2%, respectively, for the placebo group. For each week that an assessment was done, the reduction in the G-SAS total score for the paroxetine group was greater than for the placebo group, and by the end of the study the mean G-SAS total score had decreased 52% in the paroxetine group as compared to just 23% in the placebo group. The gambling urge subscale of the G-SAS, which measures intensity, frequency, and duration of gambling urges, had decreased 37.9% for the paroxetine group at study endpoint, compared to a decrease of only 19.9% for the placebo group.

Despite these impressive numbers, by the study's conclusion, the percentage (relative to baseline) of weekly income lost by gambling in the previous week was reduced by just 20.2% for the paroxetine group. For the placebo group, there was a 12.2% reduction in weekly gambling losses compared to baseline. The difference between the two groups was not significant. The authors discount the discrepancy between the minimal reduction in gambling losses and the significantly positive findings reflected in their measures of assessment. They assert that monies lost as well as frequency of gambling do not reflect gambling symptom severity accurately. They believe that gambling frequency and amounts lost reflect money availability and income, not urges and desire to gamble. The reader could counter that this modest reduction in gambling losses casts doubt both on the significance of the study findings and on the validity of the G-SAS and CGI as meaningful outcome measures.

Opioid antagonists

Crockford and el-Guebaly (1998) published a single-case report on the use of the opioid antagonist naltrexone (ReVia) to reduce gambling cravings. The patient was a 49-year-old male with a 13-year history of alcohol dependence and a nine-month history of pathological gambling (primarily video lottery terminals). He was initially prescribed fluoxetine (Prozac) for depression and enrolled in a day treatment program that addressed both addictive disorders. The patient also attended two gambling support groups, continued with AA, and made financial reparations. Despite improvement of his mood and one month of abstinence from both alcohol and gambling, he continued to experience strong cravings for gambling and drinking. He was started on naltrexone 50 mg daily and within 48 hours he described a cessation of his cravings. This was maintained over the next four weeks, and there were no relapses during this period. No further follow-up was provided.

Kim (1998) published a preliminary report of 15 patients with impulse control disorders treated with naltrexone. Of the three case reports presented to illustrate efficacy, one was a 55-year-old pathological gambler who was both a compulsive shopper and a severe slot machine gambler. There was no change during the two weeks he was on a 50 mg per day dose. Within a few days of increasing to 100 mg per day, he reported a cessation in anticipatory excitement when driving to and entering a casino. While there he had no urge to gamble, and thereafter had no cravings or difficulty abstaining. The compulsive shopping symptoms also disappeared. The patient's experience is described in his own words, lending immediacy and conviction to the report of his successful treatment.

Based on experience treating these and other patients with impulse disorders, as well as his review of the literature, Kim concluded that the 50 mg dose of naltrexone used in clinical trials for various disorders is ineffective except for patients with alcohol dependence. He found that the dose has to be titrated upwards, with most patients responding in the 100 mg to 200 mg range. Kim ends his paper by noting that most of these impulsive behaviors are pleasurable for the individual and patients may not wish to give them up. He cautions that the utility of naltrexone may be limited to those who are motivated for treatment.

Kim and Grant (2001) then conducted an open study to determine the short-term (6-week) efficacy and safety of naltrexone in treating pathological gamblers. Subjects with another Axis I disorder and those attending GA or in any kind of therapy were excluded. Seventeen subjects (7 male, 10 female) were enrolled; they averaged a DSM-IV score for pathological gambling of 8.5. Measures of efficacy were the G-SAS and the patient and clinician versions of the CGI. Naltrexone was begun at 25 mg/day for the first two days, then the dose was raised 50 mg each week until a clinically optimal therapeutic dose was reached or

to a maximum daily dose of 250 mg. If unpleasant side effects appeared, the dose was decreased until they were controlled. Three subjects were terminated from the study in weeks two and three because they could not tolerate the medication (side effects included nausea, diarrhea, increase in alkaline phosphatase). The average dose for effective symptom control was 157 mg/day. Of those who responded favorably, most did so by the end of the fourth week. By week six, when the study ended, most subjects had stopped gambling. Given the short duration of the study, the authors consider the possibility that improvement may have been a placebo response. In support of the benefit being due to the medication, they note that three months post study two of the gamblers who had been free of gambling symptoms tried to discontinue their naltrexone, only to start gambling when the dose was lowered to 50 mg. They became abstinent again when the medication was increased.

The first controlled study of naltrexone was a double-blind, 11-week trial conducted by Kim, Grant, Adson and Shin (2001b). Subjects met DSM-IV criteria for pathological gambling (average score 8.1), but were excluded if they had a current Axis I diagnosis, had abused alcohol or drugs within the previous three months, or had a severe personality disorder (e.g. borderline or antisocial). The majority of subjects were women, and slot machines were the most common form of gambling. After a one-week placebo lead-in, naltrexone was started at 25 mg/day and titrated upward until maximum symptom improvement or until the dosage reached 250 mg/day. Out of 83 subjects enrolled in the study, data from 45 patients were analyzed. These 45 completed week six, which corresponded with two weeks of naltrexone at 100 mg/day. Twenty of the 45 had been randomized to naltrexone. Despite the high dropout rate, it should be noted that most subjects tolerated the medication quite well. The largest number of subjects (n=22) was terminated due to a significant placebo response (50% improvement or greater) during the first week placebo lead-in.

Symptom change was assessed using the G-SAS and clinician- and patient-rated versions of the CGI. At study end, 75% of the naltrexone-taking subjects were much or very much improved on all three measures, as compared to 24% of those on placebo. While this is a lower standard than abstinence, it is still impressive. The average dose of naltrexone at the end of the study was 188 mg/day. The only side effects reported were nausea in the first week of treatment and an increase of liver enzymes in patients concurrently taking analgesics. It is worth noting that the subjects who had moderate or higher levels of urge symptoms at baseline responded better to the medication. The authors concluded that pre-treatment severity of gambling urges may identify naltrexone responders, and that using this as a stratification variable should improve group outcome. (There is support for this from studies of alcoholics treated with naltrexone; e.g. Jaffe et al., 1996; Monterosso et al., 2001.) However, since Kim and his colleagues only measured

weekly average urge symptoms, little could be said about the temporal or causal relationship between urges and gambling behavior. Nonetheless, they also observed that, in addition to reducing urges to gamble, naltrexone reduced the subjective experience of pleasure when subjects did gamble.

Despite the safety demonstrated by Kim's study, some clinicians may be put off by the FDA's “black box” warning of potential liver damage when naltrexone is used in doses greater than 50 mg/day. Kim, Grant, Adson and Remmel (2001a) believe this to be due to a drug interaction. They caution patients about using analgesics while on naltrexone, and they also closely monitor for hepatotoxicity. They recommend liver function tests prior to starting the medication, then at two- to four-week intervals for the first three months, monthly for the next three, and then every three to four months (Grant & Kim, 2002).

Mood stabilizers

In 1980, just prior to the introduction of pathological gambling in DSM-III, Moskowitz published an article entitled, “Lithium and Lady Luck.” He described the treatment of three compulsive gamblers with lithium carbonate (1800 mg/day). Significant abstinence was achieved in all three cases, with marked improvement documented by long-term follow-up. However, it is important to note that two of the patients were clearly bipolar, and the third probably so.

Haller and Hinterhuber (1994) published a double-blind, controlled study (12 weeks each phase) of one gambler treated with carbamazepine (Tegretol). The patient's gambling continued while on the placebo with no improvement, but he became abstinent on carbamazepine by week two and did not gamble for the duration of the trial. In fact, he remained abstinent on open maintenance (600 mg/day) through the two and a half years he was followed. The results are particularly impressive given his prior history of treatment failures. Despite years of behavior therapy, psychoanalysis, and GA, his longest previous period of abstinence had been three months. Carbamazepine is an anticonvulsant that has been used as a mood stabilizer, particularly in patients with bipolar disorder. There is no mention in the report of cyclothymia or emotional instability. We are told only that the patient played roulette to relieve stress and depression. An EEG showed “minimal nonspecific abnormalities,” while an extensive neurological evaluation was normal.

Pallanti, Quercioli, Sood and Hollander (2002) conducted the first controlled trial of mood stabilizers for the treatment of pathological gambling. Forty-two pathological gamblers (32 male, 10 female) were enrolled in a 14-week, randomized, single-blind study of lithium and valproate. Subjects with bipolar disorder were excluded, as were those with schizoaffective disorder, schizophrenia, organic illnesses, and comorbid alcohol or drug addiction. None of the subjects received psychosocial or supportive therapies during the trial.

The lithium group was given 600 mg/day for the first four days, 900 mg/day for days five through nine, then up to 1200 mg/day for the remainder of the trial. The second group received 600 mg/day of divalproex sodium for the first five days, and then up to 1500 mg/day. Titration upward for both groups depended upon weekly plasma levels and how well the medications were tolerated. At the end of the 14 weeks, both groups showed significant improvement on the PG-YBOCS. According to the CGI, 14 (60.9%) of the 23 subjects taking lithium and 13 (68.4%) of the 19 subjects taking valproate were much or very much improved. It should be noted that eight of the nine lithium nonresponders dropped out of the study (six due to noncompliance, two due to side effects). Only three of the 19 subjects on valproate dropped out. The authors speculate that a possible reason for this discrepancy is valproate's known anxiolytic effect.

The researchers tried to exclude pathological gamblers with bipolar disorder, so that a decrease in gambling behavior would not be attributed to treatment of the comorbid mood disorder. In this they may have been only partly successful, as they acknowledge that use of the SCID as their primary diagnostic instrument may have allowed subjects with bipolar II and other subtle mood disorders to enter the study. They recognize the overall preliminary nature of their results, and call for a double-blind, placebo-controlled trial to confirm their findings.

Methodological and other considerations

How best to measure outcome remains uncertain, and this is clearly something with which gambling researchers are grappling. For example, in the study we just discussed (Pallanti et al., 2002), one of the two outcome measures, the PG-YBOCS, showed a mean behavior score reduction from 11.9 to 8.6 for the lithium group and an 11.0 to 7.0 reduction for the valproate group. While statistically this improvement is considered significant, for the individual gambler it may mean a reduction from seven hours a day of video poker to three hours a day, or from three nights a week of gambling to one night a week. Similarly, Kim's double-blind paroxetine study reported impressive reductions in the CGI and G-SAS scores for the medication group, but only a 20% reduction in amounts of money lost. It is questionable whether family members would agree with the authors in calling these treatments successful.

One also cannot help wondering about the stability of such results. Patients who abstain from alcohol (O'Malley et al., 1996) and cocaine (Carroll et al., 1994) while being treated with naltrexone have a significantly better long-term outcome than those who only reduce the amounts they drink or use. Are severe pathological gamblers who reduce but do not stop gambling as likely to maintain their improvement as those who achieve abstinence? This is a question to be asked of all clinical trials that take reduction of gambling or overall subjective improvement as their goals, as opposed to abstinence, which is favored by GA and most

clinicians.

It is noteworthy that most studies found a strong early placebo response in pathological gamblers. This corresponds with something one often observes clinically. Pathological gamblers are often good beginners. While they may start therapy, jobs, or relationships with enthusiasm, they have difficulty staying the course. One must be cautious about clinical trials of only a few weeks or months. Furthermore, an experience shared by clinicians treating a variety of disorders is that SSRIs sometimes seem to lose their effectiveness toward the latter part of the first year and during the second year.

Whenever naltrexone has been used to treat addictive disorders, problems with compliance have limited its efficacy. For example, Greenstein et al. (1981) found that less than 10% of patients who began naltrexone treatment for opioid dependence were still taking the medication after two months. The best results with alcoholics were obtained in highly motivated subjects, such as doctors and other professionals, in mandated treatment programs (Washton, Gold & Pottash, 1984). The long-term use of naltrexone for pathological gamblers raises similar issues about compliance. Motivation for staying on the medication may wane for a variety of reasons. Patients may miss gambling, become distracted or overwhelmed by problems avoided while they were gambling, or become overconfident about their recovery. According to the alcoholism literature (Pettinati, Volpicelli, Pierce & O'Brien, 2000), patients who took less than 80% of their pills had outcomes no better than if they were on placebo. Kim has patients divide their dose once they are on 100 mg/day or more (Kim et al., 2001a). Since most do not respond until 150 mg is reached, that means that most gamblers are taking it twice daily. Even if only taking it once a day, patients can forget to take their medication, skip doses, or rationalize cutting down in anticipation of a return to gambling. A follow-up of alcoholics treated with naltrexone found that, when patients stopped taking the medication, they relapsed to pre-treatment levels of addiction (O'Malley et al., 1996). Therefore, follow-up at six months and one and two years is needed. None of the gambling studies to date address questions of how long patients should remain on medication, or about intermittent versus long term use. The authors acknowledge the preliminary nature of their findings and the need for further studies addressing the questions they raise.

Kim (personal communication, June 25, 2001) followed up his naltrexone responders and found that almost all of them wanted to stay on the medication, but were unable to because insurance did not cover it. The retail price of ReVia is between $695 and $925 (US) a month for the dosage found effective (150–200 mg); generic naltrexone would cost between $570 and $760 (US) a month. When possible, Kim keeps patients on naltrexone for two to three years, then attempts to stop the medication. If their gambling urge returns, he has them resume

naltrexone. He most often combines naltrexone with an SSRI, and, when necessary, combines it with cognitive behavioral therapy. Results are good, he states, and abstinence is maintained when patients stay on naltrexone. However, he has found that patients frequently drop out of treatment after three to six months. Those patients are lost to follow-up.

There are no studies on the treatment of pathological gambling which look at combinations of medication, although the practice of combining naltrexone with an SSRI was found safe in a large scale multi-site trial involving alcoholics (Croop, Faulkner & Labriola, 1997). Nor are there studies looking at medication combined with psychotherapy, or comparing brief psychotherapy and/or educational interventions with medication. For the type of subject found in most clinical trials (absence of comorbidity, reasonable motivation), this latter approach might be efficacious. We would also like to see a study in which naltrexone is administered to those who are actively gambling, as opposed to those who are trying to avoid relapse. Sinclair (1998) has advocated such an approach with alcohol dependence. A sustained release or depot form of naltrexone has been in development. Nalmefene, an opioid antagonist structurally similar to naltrexone, is being tested in a multi-site study of pathological gamblers.

Several of the pharmacotherapy studies are promising. However, until they are expanded and replicated their results must be thought of as preliminary. An editorial in the *New England Journal of Medicine* (Fuller & Gordis, 2001) reminds us that “as the value of any medication is being established, randomized clinical trials are not always consistent in their findings.” The example they discuss is the use of naltrexone for treating alcohol dependence. While initial reports were enthusiastic, larger studies (Kranzler, Modesto-Lowe & Van Kirk, 2000; Krystal, Cramer, Krol, Kirk & Rosenheck, 2001) found the medication no more effective than the placebo. However, the daily dosage of naltrexone was 50 mg, and participation in the studies was not dependent on the presence of cravings. In these studies, clinicians find a “small to medium effect” (Litten, 2002), with success dependent on the careful selection of patients. Still, there is a tendency to think that each new medication will be a wonder drug. The reality is that subsequent studies often do not bear out initial findings, side effects are discovered, expectations lowered, but these same less-than-perfect drugs still have a useful place in our armamentarium.

Models for treatment with medication

Strictly speaking, there is no medication that is “anti-gambling” and given the importance of uncertainty and risk in everyday life, it is unlikely there will be. Furthermore, when considering treatment strategies it may be a mistake to think of pathological gamblers as a homogeneous group. There are a number of models

that have potential for helping the clinician tailor specific medications to individual patients. These include treatment strategies that address pathological gambling in terms of (1) neurotransmitter depletion/imbalance, (2) kindling, (3) withdrawal, (4) cravings, (5) comorbidity and (6) subtyping.

Neurotransmitter depletion/imbalance

Chronic cocaine use causes a dopamine deficiency, which has been thought to be the basis for acute cravings and prolonged anhedonia and anergia (Dackis, Gold, Davies & Sweeney, 1985; Washton, 1989). Strategies for treating cocaine users have concentrated on a number of dopaminergic agents, with mixed results. These have included amantadine, bromocriptine, pergoline, methylphenidate, L-dopa, mazindole, buproprion, and flupenthixol (Kleber, 1995). Chronic use of marijuana or nicotine also causes a depletion of dopamine. The only FDA approved anti-smoking medication other than nicotine replacement therapies is the dopaminergic antidepressant buproprion (Wellbutrin, marketed for this purpose as Zyban).

While prolonged use or exposure to an addictive substance or activity may cause depletion of dopamine or other neurotransmitters, it is also possible that the deficiency occurred first and creates the vulnerability for addiction. This primary deficiency could be related to genetic factors, early trauma or other environmental conditions, or another disorder such as depression. Erickson (1996) and others have hypothesized that the various forms of substance dependence are associated with different neurotransmitter deficiencies. An alcohol-dependent individual, according to the theory, lacks normal concentrations of one or more neurotransmitters in the median forebrain bundle (the so-called “pleasure center”) of the brain. They drink to feel “normal,” meaning to elevate their neurotransmitters to normal levels. Preliminary research on pathological gambling has found deficits in the serotonergic, noradrenergic, and dopaminergic systems.

Pharmacological challenge tests stimulate neuroendocrine and behavioral responses in patients and control groups as a means of assessing 5-HT receptor function (Murphy, Mueller, Garrick & Aulakh, 1986). Investigators have found both blunted and enhanced response to serotonergic probes in pathological gamblers. Moreno et al. (1991) reported blunted prolactin response to intravenous clomipramine suggesting serotonergic receptor *hyposensitivity*. On the other hand, DeCaria et al. (1996; 1998a) found an enhanced prolactin response following oral administration of a single dose of m-CPP, a metabolite of trazodone with high affinity for serotonin receptors. Their results suggest serotonin receptor *hypersensitivity*. This may represent decreased serotonin availability and/or release associated with subsequent up-regulation of the serotonergic postsynaptic receptors. DeCaria et al. (1998a) also found that m-CPP stimulated a “high” in their subjects that resembled their experience while gambling. A similar finding has been found in subjects with trichotillomania (Stein, Hollander, Cohen, Simeon &

Aronowitz, 1995), alcohol dependence (Benkelfat et al., 1991; Krystal, Webb, Cooney, Kranzler & Charney, 1994), cocaine dependence (Buydens-Branchey & Branchey, 1993), and borderline personality disorder (Hollander et al., 1994).

Other studies that implicate serotonin have measured platelet MAO activity. This peripheral marker of serotonergic function was lower in pathological gamblers (Carrasco et al., 1994; Blanco et al., 1996). Decreased MAO activity has been correlated with high sensation-seeking behavior (Fowler, von Knorring & Oreland, 1980; Ward, Catts, Norman, Burrows & McConaghy, 1987). Carrasco's group found this correlation; Blanco's did not. The difference may be a function of their subject selection. However, no information is given about gambling histories or forms of gambling engaged in by either group.

A third way to examine serotonin activity is by measuring its metabolites in cerebrospinal fluid. Here the results are mixed. The metabolites 5-HT and 5-HIAA in the CSF of pathological gamblers were unchanged in two studies (Roy et al., 1988; Roy, De Jong & Linnoila, 1989; Bergh et al., 1997). However, when flow rates were corrected, Nordin and Eklundh (1999) found decreased rates of 5-HIAA in the CSF of male pathological gamblers.

The cited studies by Roy et al. (1988, 1989) and Bergh et al. (1997) did find evidence of increased noradrenergic activity. The former found the metabolite of noradrenaline, MHPG, increased in the CSF of pathological gamblers, while the latter confirmed this finding and also reported an increase in the concentration of noradrenaline. Further evidence of noradrenaline involvement in pathological gambling comes from DeCaria et al. (1996, 1998a), who found increased growth hormone in response to oral clonidine (an alpha-2 receptor agonist) challenge.

The primary focus of the Bergh study, however, was dopamine function. The authors reported that concentrations of dopamine were lower in the CSF of pathological gamblers as compared with controls, but that levels of its metabolites, dihydroxyphenylacetic acid (DOPAC) and homovanillac acid (HVA), were higher. These findings suggest increased release of dopamine in the brain. The ratios between DOPAC or HVA and dopamine were significantly higher for the gamblers. This could be a consequence of their gambling or it could point to a prior dopamine deficiency that would make them vulnerable to a gambling addiction.

In the first genetic study of pathological gamblers, Comings et al. (1996) demonstrated that, compared with controls, gamblers were significantly more likely to have the A1 allele for the dopamine D2 receptor gene. The more severe the gambling pathology, the more likely they were to possess the abnormality. The authors emphasized that pathological gambling is not a single gene disorder, and that mutant genes are not disease-specific but, rather, associated with a spectrum of interrelated disorders. However, their significant findings could not be accounted

for by comorbid conditions.

Parkinson's disease, which is caused by the loss of dopamine-producing neurons in the substantia nigra, and which is treated with dopamine agonists (pergolide, ropinirole) or replacement (levodopa), offers a natural opportunity for observing the role of this neurotransmitter. Iatrogenic pathological gambling has been reported in Parkinson's patients treated with the above-mentioned dopaminergic drugs (Molina et al., 2000; Seedat, Kesler, Niehaus & Stein, 2000; Gschwandtner, Aston, Renaud & Fuhr, 2001). The gambling behavior seems to coincide with the overuse of these medications and to cease when doses are reduced.

Goyer et al. (1999) presented the first positron emission tomography (PET) scans of pathological gamblers. They showed significant hypofrontality, which the authors correlated with deficits in attention and executive function elicited through cognitive testing. Findings of decreased D2-like indices consistent with a hyperdopaminergic state lend further support to a key role for this neurotransmitter.

Since serotonin has been implicated in the regulation of impulsivity and compulsivity, noradrenaline in the mediation of arousal and novelty seeking, and dopamine in reward and reward dependency, the above findings, albeit preliminary, are of significance. De Caria (personal communication, October 17, 2001) believes that all three neurotransmitters are involved in pathological gambling, but at different stages of the gambling cycle. Thus, anticipatory arousal may be linked to the noradrenergic system, the “high” of the actual gambling episode associated with the serotonergic system, and difficulties extinguishing the behavior under the aegis of the dopaminergic system.

Kindling

Kindling is a neurophysiological mechanism first described in animals by Goddard, McIntyre and Leech (1969). They found that a recurrent, subthreshold stimulus applied over time can produce a progressively exaggerated response, with long-term or permanent changes in brain function. Their experiment consisted of stimulation of the amygdala for one second or less a day at an intensity unlikely to effect electrical or behavioral change. After a few weeks, the stimulus would culminate in a major motor seizure. Once such seizures have developed, they can be evoked again months or years later even if the animal has had no further stimulation in the interim (Wada, Sato & Corcoran, 1974; Racine, 1978). Thus, the kindling process appears to involve permanent changes in neural excitability. After a sufficient number of amygdala-kindled seizures, spontaneity will develop (Wada et al., 1974) and the animal will continue to have full-blown, generalized convulsions in the absence of electrophysiological stimulation. Neuronal sensitization has applicability not only as a model of epilepsy but for learning and memory (Goddard et al., 1969; Goddard & Douglas, 1975). Kindling has been

invoked to explain disorders characterized by episodic, progressive symptomatology, notably bipolar disorder (Ballenger & Post, 1978a, 1980) and addiction (Ballenger & Post, 1978b; Halikas, Kuhn, Carlson, Crea & Crosby, 1992; Adinoff, O'Neill & Ballenger, 1995; Berridge & Robinson, 1995).

Ballenger and Post (1978a, 1980) noted the similarity between kindling and the progression in manic-depressive disorder. They hypothesized that carbamazapine, an anticonvulsant found to block amygdala-kindled seizures in animals, could benefit patients who were manic-depressive. Dalby (1971, 1975) had earlier reviewed 2500 epileptic patients treated with carbamazepine, and found that half showed improvement in mood and behavior independent of its effect on seizure control. Limbic substrates had previously been implicated in the modulation of affect (Papez, 1937; Isaacson, 1974; see review in Post, Uhde, Putnam, Ballenger & Berrettini, 1982).

Ballenger and Post's hypothesis was correct, and the anticonvulsants carbamazepine (Tegretol) and valproate (Depakote) and more recently lamotrigine (Lamictal), gabapentin (Neurontin), and topiramate (Topamax) have proven themselves effective in the treatment of bipolar disorders, especially the soft spectrum, the mixed states and rapid cyclers, and the cases that fail to respond to lithium. The time course for mood stabilization is several weeks, suggesting that the mechanism of action is different from the rapid anticonvulsant effect of these drugs (Post et al., 1982; Post, 1990). However, stabilization of the limbic system may still be taking place.

Kraepelin (1921) was one of the first to observe that the interval between episodes of an affective disorder gets shorter as the disease progresses. A number of studies (Post, Rubinow & Ballenger, 1986; Tohen, Waterneax & Tsuang, 1990; see review in Post, 1990) have since documented the potential for the disorder to speed up in cycle frequency, severity of episodes, and rapidity of onset of individual episodes. Post (1990) predicted, based on the kindling and sensitization model, that psychosocial precipitants or exogenous stressors would be more apparent in the initial episodes, but would then become less obvious until, with sufficient repetition, episodes become autonomous. The model also predicted that the effectiveness of pharmacotherapy would be a function of the course of the disorder, and, in fact, lithium is more effective in the earlier phases. If rapid cycling and mixed states develop, patients may become refractory to lithium carbonate.

Progression, then, in the bipolar disorders is characterized by (1) a progressively shorter interval between episodes, (2) increasingly greater severity of episodes, (3) decreasing need for an environmental event or trauma to trigger the episode (leading to “spontaneity”), and (4) decreasing effectiveness of medication. Unipolar depressions may follow a similar progressive course. This has lead to an aggressive approach to medication in which treatment is instituted early and

maintenance medication is used prophylactically. Once medication is stopped it may not be effective when reinstated or may require an upward dosage adjustment.

Attempts to apply the kindling model to addiction have mainly focused on cocaine (Halikas et al., 1992) and alcohol dependence. Ballenger and Post (1978b) suggested that repeated episodes of alcohol withdrawal act as a limbic stimulus. Not only is there a lowering of the seizure threshold, so that there is an increase in occurrence of delirium tremens and in the severity of withdrawal symptoms, but they also hypothesized that the repeated experience of withdrawal could result in pathological behavior during periods of abstinence. Adinoff et al. (1995) reviewed the literature, and argued that repeated episodes of alcohol withdrawal result in a state of permanent limbic excitability that can lead to spontaneous withdrawal-like symptoms during periods of abstinence. These are experienced as anxiety and they are associated with urges or cravings to drink and are an important factor in relapse. Studies are cited in support of their hypothesis that it is not the chronic consumption of alcohol that determines the severity of cravings, but the frequency and severity of withdrawal episodes.

It would be important to determine whether part of the progressive nature of pathological gambling consists in increases in withdrawal symptoms, greater affective instability, and greater frequency and intensity of cravings. It would also be important to evaluate whether external stressors play a progressively diminished role, with seemingly autonomous episodes occurring later in the disorder. There are studies demonstrating that pathological gamblers become increasingly impulsive as the disorder progresses (Rugle & Rosenthal, 1993; Rugle, Rosenthal & Lesieur, 1996). Additional research, in particular, longitudinal studies, might provide data supporting aggressive treatment and the early use of medication as has been shown to be warranted for bipolar disorder.

Withdrawal

There are several studies that describe withdrawal symptoms in pathological gamblers (Wray & Dickerson, 1981; Meyer, 1989; Rosenthal & Lesieur, 1992). According to the survey by Rosenthal and Lesieur, (n=222), physical symptoms were prominent, including insomnia (50%), headache (36%), upset stomach or diarrhea (34%), physical weakness (27%), heart racing or palpitations (26%), shaking (19%), muscle aches or cramps (17%), difficulty breathing (13%), sweating (12%) and chills or fever (6.5%). None of these symptoms correlated with gender, type of gambling, extent of alcohol or drug use while gambling, or self-described alcohol or drug dependence. They did correlate with number of hours spent gambling, severity of the problem as measured by DSM-IV criteria, and presence of dissociation. However, these symptoms were self-limited. We have yet to find a gambler who needed to be medicated for their withdrawal symptoms.

Cravings

With regard to cravings, pathological gamblers seem to fall into three groups. Some quickly put gambling behind them once they start dealing with whatever it is from which they had been trying to escape. From the beginning of treatment they experience no thoughts or urges to gamble. Others will have sporadic cravings in response to specific cues and when certain issues emerge in therapy. A third group of patients will have frequent and intense cravings with which they wrestle daily. Differences between the three groups are a topic for future research, as is the relationship between cravings and relapse to gambling.

The following four approaches to a pharmacotherapy of cravings seem worth exploring:

Drug hunger (and the use of substitution agents)

Substitution agents take away hunger by satisfying it (Dole & Nyswander, 1965). Accordingly, the experience of withdrawal is subjectively experienced as craving. This is also a dehydration-thirst model. A well-known substitution agent from the field of chemical dependency is methadone.

Blocking agents

These are compounds that block the excitement or pleasure of the addictive drug. The best known example is the opioid antagonist naltrexone. When the medication works, it seems to do so early, probably by reducing urges. It is not clear whether this is some direct pharmacological effect, or whether it is because patients know that the drug or behavior will not work for them and this knowledge psychologically reduces cravings. In general, addicted individuals sequestered as inpatients usually experience a rapid reduction in cravings (Margolin, Kosten & Avants, 1992). When released to an environment in which drugs are available, they frequently experience intense cravings and relapse. Meyer and Mirin (1982) emphasized the role of perceived availability. Naltrexone makes the drug unavailable, not physically, but in terms of its effect. The result is a kind of “why bother?” One would expect that the blockade would have to be subjectively experienced; and that, therefore, one or more slips would need to occur as part of the learning process. Since one-trial learning is improbable, a number of episodes would be expected. This is at odds with the prior observation that naltrexone, when effective, works almost immediately to reduce cravings and use.

A drug that blocks the excitement of an addictive drug or activity would hold great promise for the treatment of pathological gambling. As described above, there are two single-case reports (Crockford & el-Guebaly, 1998; Kim, 1998) and two clinical trials (Kim & Grant, 2001; Kim et al., 2001a) pursuing this approach. Positive results are reported, but the studies involved small samples and a short duration of

treatment. Kim (1998) also described a successful outcome for a compulsive shopper and the reduction of urges for a patient with kleptomania. He cites clinical reports on the treatment of a number of other impulse disorders, including the paraphilias, bulimia, trichotillomania, repetitive self-mutilation and obsessive-compulsive disorder. For most of these disorders naltrexone was not very effective.

"The thrill is gone!" This is the characteristic experience of the drug-addicted person on naltrexone. It is the absence of this excitement that the gambler in Kim's 1998 paper so clearly described. It would be important that any naltrexone study distinguish between action-seeking pathological gamblers and escape seekers. The majority of Kim's subjects were escape gamblers. One would anticipate a much more profound effect with the action seekers. At the same time, one can also predict even greater problems with compliance. Particularly for the sensation seekers, those whose whole manner of life revolves around the pursuit of strong sensations and excitement, a medication like naltrexone could result in profound upheaval and depression. The drug does block endogenous opioids. For example, runner's high, the joy and euphoria of long-distance running, is reduced by opioid antagonists (Janal, Colt, Clark & Glusman, 1984; see also Grossman et al., 1984; Daniel, Martin & Carter, 1992). The medication is known to cause dysphoria and depression in normal and addicted subjects (Mendelson, Ellingboe, Keuhnle & Mello, 1978; Hollister, Johnson, Boukhabza & Gillespie, 1981; Crowley, Wagner, Zerbe & Macdonald, 1985). Interestingly, Kim describes a lessening of depression (Kim et al., 2001a) in his primarily female, video and slot machine gamblers.

Another group of drugs that should be considered here are the beta blockers, of which the best known are propranolol (Inderal) and atenolol (Tenormin). By decreasing autonomic arousal they block many of the physical manifestations of excitement. Although beta blockers have been around for decades, we know of no cases in which they were administered to pathological gamblers. Any study of their effectiveness should make a distinction between action seekers and escape seekers.

An obsessive-compulsive model

Modell, Glaser, Cyr and Mountz (1992) have suggested that many of the aspects of craving in the alcohol dependent individual are similar to the thought patterns and behavior of patients with obsessive-compulsive disorder (OCD). These include recurrent and persistent thoughts about alcohol, an inability to resist these thoughts, a compulsive drive to consume alcohol, and a loss of control over that drive. They modified the Yale-Brown Obsessive Compulsive Scale to measure those aspects of craving in heavy drinkers. On this same premise, similar instruments have been developed for compulsive buying (Monahan, Black & Gabel, 1996), body dysmorphic disorder (Phillips et al., 1997), and pathological gambling (DeCaria et al., 1998a).

Based on the resemblance of cravings to OCD, one would expect that medications useful in the treatment of OCD would be able to control cravings for alcohol or drugs. This has not proven to be the case. However, some gamblers who have urges or thoughts about gambling appear to ruminate or obsess about it. Medication may not reduce the urges, but may make them manageable by eliminating these secondary ruminations.

Reduction of negative affect

A trigger or cue leads to an urge to gamble, which in turn may be followed by physiological symptoms that intensify the urge or desire, and which may be acted upon. Triggers are external and “associative” (things in the environment which remind one of gambling) or internal and psychological. Typical psychological triggers are feelings of helplessness, shame and guilt. Anger is often a secondary and mediating affect. Particularly difficult situations for the gambler are those that involve uncertainty or perceived expectations and demands that stimulate feelings of inadequacy.

Medications that reduce the intensity of negative affect, such as SSRIs and mood stabilizers, could interrupt the response sequence in one of two places. Either the affect will not trigger the craving, or the gambler may still have cravings but will be better able to resist them. The details of how this occurs are not entirely clear. While taking SSRIs, patients are better able to tolerate negative affects. This may be related to a general dampening of affect: they feel less. Or it may be due to some inhibition of associative pathways: they feel as intensely but react less.

Comorbidity

Axis I disorders

Mood disorders

Comorbidity is the clearest indication for medicating pathological gamblers. Unlike alcoholics who, it is generally believed, are more apt to drink in order to medicate anxiety (see review by Clark & Sayette, 1993), gamblers show a preponderance of mood disorders and attention deficit hyperactivity disorder. In this respect they most closely resemble cocaine addicts (Rounsaville et al., 1991; Mirin, Weiss, Griffin & Michael, 1991). Three studies of pathological gamblers utilizing structured interviews (McCormick, Russo, Ramirez & Taber, 1984; Linden, Pope & Jonas, 1986; Specker, Carlson, Edmonson, Johnson & Marcotte, 1996) found lifetime rates for major depression of 76%, 72%, and 70%, respectively.

In a population of male, inpatient gamblers, McCormick's group found that 32% were bipolar (6.5% bipolar I, 26% bipolar II). Linden and colleagues interviewed male GA members and found 24% with bipolar disorder. Specker et al. studied a

population of outpatient gamblers, 40% of which were female, and a significant percentage of which were slot, video poker and pull-tab gamblers. They found that only 5% of this group were bipolar, but of the 70% with histories of major depression, the onset of the depression preceded the onset of problem gambling in two-thirds of their subjects. According to a general population survey done for the National Gambling Impact Study Commission (Gerstein, Volberg, Harwood & Christiansen, 1999), one-third of the pathological gamblers had had at least one manic episode and 20% to 29% had had a major depressive episode. This last study, it should be emphasized, was conducted on a nontreatment population. The authors concluded that the lifetime prevalence for major mood disorders was clearly higher for problem and pathological gamblers than for the general population. They also noted that it correlated with the severity of the gambling disorder. Becoña, del Carmen Lorenzo and Fuentes (1996) reported similar findings.

The association between bipolar disorder and pathological gambling should come as no surprise. Bipolar disorder is the Axis I disorder most commonly associated with substance abuse and dependence (Regier et al., 1990; Brady & Lydiard, 1992; Kessler et al., 1997; Strakowski & DelBello, 2000). Over half the individuals with bipolar disorder have problems at some time in their lives with substance abuse, especially alcoholism and cocaine abuse or dependence (Regier et al., 1990). Conversely 20% to 30% of treatment-seeking cocaine abusers met lifetime criteria for a bipolar spectrum disorder (Gawin & Kleber, 1986; Mirin, Weiss, Michael & Griffin, 1988; Nunes, Quitkin & Klein, 1989; Rounsaville et al., 1991). Research is needed to examine more closely the similarities between pathological gambling and cocaine abuse. For example, it is known that cocaine is most frequently used by cyclothymic and bipolar patients to intensify and lengthen their euphoric mania rather than to self-medicate depressive episodes (Weiss & Mirin, 1987; Weiss, Mirin, Griffin & Michael, 1988; Brady & Lydiard, 1992). It is not known whether this is true for gambling.

Just as stimulant intoxication can produce a syndrome indistinguishable from mania or hypomania, it is well known that pathological gambling can mimic criteria for bipolar disorder. It seems most reasonable to diagnose a primary mood disorder only if it occurs before the onset of pathological gambling or during periods of remission. However, therapists faced with the dual diagnosis patient do not usually have the luxury of waiting for periods of remission. Family history is important.

Adding to the complexity of diagnosis and treatment may be comorbid substance abuse and dependence in the gambler (50% lifetime prevalence according to Ramirez, McCormick, Russo & Taber, 1984; Linden et al., 1986; Lesieur & Blume, 1991a) and the likelihood of spectrum and more subtle mood disturbances

contributing to the gambling problem. According to Akiskal (1987; Akiskal & Mallaya, 1987), the soft spectrum bipolar disorders, including cyclothymia and bipolar II, are several times more common than the traditional bipolar I. At least some researchers (Akiskal, 1992; Marlowe et al., 1995) believe that substance abusers, perhaps especially those dependent on cocaine, are more likely to be self-medicating for subsyndromal cyclothymic or dysthymic symptomatology than for major episodes.

There is little information available about the treatment of pathological gamblers with comorbid bipolar disorder. We cited a case series on the successful use of lithium with bipolar gamblers (Moskowitz, 1980) and a controlled trial of lithium and valproate (Pallanti et al., 2002). In the latter study, as in most clinical trials of pathological gamblers, anyone with bipolar disorder was excluded. It should be noted that the DSM-IV criteria for pathological gambling have a partial exclusion for gambling which only occurs during a manic episode and, in the clinician's judgment, is better explained by the latter disorder. This has been somewhat controversial as there was no research to justify its addition to the criteria, and no subsequent studies in support of its retention.

One can reasonably assume that patients with bipolar disorder who are pathological gamblers will require more hospitalizations and do less well in treatment than those who are not gamblers, and that pathological gamblers who are bipolar have a worse prognosis than those who are not bipolar. But again there is no data to support either of these statements, and there is much about the relationship between the two disorders that we do not know.

Noted at the beginning of this section were significant rates of depression among pathological gamblers. That data was obtained from treatment populations, where one would expect to find greater comorbidity. Alcoholics (Helzer & Pryzbeck, 1988), opiate addicts (Rounsaville & Kleber, 1985; Brooner, King, Kidorf, Schmidt & Bigelow, 1997), and cocaine abusers (Rounsaville et al., 1991; Carroll & Rounsaville, 1992) who have symptoms of depression are more likely to seek treatment. A regularly asked question has to do with whether the depression is primary or secondary. In the author's experience, it is frequently both. Individuals may gamble to self-medicate chronic dysphoria or a primary depression, but the consequences of their gambling cause an acute, secondary depression.

The depression of the pathological gambler in outpatient or inpatient therapy is often masked. The patient may appear to be getting better and not show overt signs of being depressed, but psychological testing will reveal a surprising degree of depression. There may be several reasons for this. Many gamblers have learned how to “act normal.” They may be very good at figuring out what other people want or expect from them in order to be accepted. Or they may be so desperate to believe they are better that they deceive themselves. This is the

"wishing will make it so" type of thinking that led them to believe they could win back gambling losses and solve all their problems by continuing to gamble. Confronting these deceptions and self-deceptions is an important part of therapy. All too often, however, the depression goes unrecognized and, therefore, untreated. Hand (1998) has made a similar observation. Many of the pathological gamblers they see in Germany are not aware they are depressed.

Attention deficit hyperactivity disorder

Another Axis I disorder showing significant comorbidity with pathological gambling is attention deficit hyperactivity disorder (ADHD) (Carlton et al., 1987; Carlton & Manowitz, 1994; Rugle & Melamed, 1993; Castellani & Rugle, 1995; Specker, Carlson, Christenson & Marcotte, 1995; Littman-Sharp & Jain, 2000). This research parallels reports of ADHD in people with other addictions (Rounsaville et al., 1991; Wilens, Biederman, Spencer & Frances, 1994; McCance-Katz, Leal & Schottenfeld, 1995). Rugle (1995) conducted structured interviews on 60 inpatient male pathological gamblers. Using Wender's (1995) narrow criteria, 34% of her sample was diagnosed with ADHD. When broader criteria were used, as Wender recommends when reliable collateral criteria are not available, the percentage increased to 48%. Ozga and Brown (2000) found that 32% of 50 (25 male, 25 female) VLT/slot machine pathological gamblers met the Conners' criteria (Conners, Erhardt & Sparrow, 1998) for adult ADHD. They had higher scores on inattention than on hyperactivity or impulsivity. Those with ADHD showed greater gambling severity. Specker et al. (1995) conducted structured interviews on 40 pathological gamblers (25 male, 15 female) from an outpatient treatment program. Attention deficit disorder was diagnosed in 20% of the gamblers while another 18% missed threshold criteria by only one item. ADD was more common in male gamblers, but the gender difference was not significant.

Research comparing pathological gamblers to substance abusers found gamblers to be significantly more impulsive, both cognitively and behaviorally (Castellani & Rugle, 1995). The gamblers scored in the normal range for excitement seeking, thus it appears that they were more likely to engage in risk-taking behavior as a result of a lack of planning and forethought rather than from any conscious seeking out of exciting or risky situations. The gamblers also scored significantly lower than the alcoholics or cocaine addicts on the NEO Personality Inventory Conscientiousness Scale, reflecting their inability to organize, plan, and follow through on goals.

The ADHD gambler's description of how he or she uses gambling to self-medicate is similar to that of the cocaine abuser with comorbid ADHD. At least in the beginning, gambling focuses (hyperfocuses) their attention, allowing them to slow down, concentrate and feel normal. It alleviates boredom and restlessness. In addition, it offers the opportunity for spectacular success (the big win), which is

thought to provide recognition and self-esteem. The ADHD gambler often has a history of failure, and believes that nothing he or she does is good enough or is ever enough. The simplicity and polarity of the win/lose orientation of gambling also offers a way to organize one's life, seeming to bring clarity, structure, and a solution to problems.

As one would expect, ADHD significantly complicates the life of the pathological gambler, and unless recognized and treated, worsens prognosis. The ADHD gambler may be particularly skillful at secrecy and deception, having learned early in life how to cover up attention problems. He or she has a strong sense of shame at feeling different, inadequate, and stupid; has had only limited success following traditional paths to achievement; and often feels fraudulent even when successful. Gamblers with ADHD have difficulty making connections between what they do and why they do it. In treatment, they are often forgetful, impulsive and self-destructive. They frequently have difficulty setting and adhering to goals. ADHD gamblers typically have difficulty learning from experience and, in particular, connecting cause with effect. Their attention problems interfere with their ability to handle cravings, as it is difficult for them to direct their attention away from these high intensity but unwanted thoughts. A strong case can be made for the use of medication in treating the ADHD pathological gambler. However, they may like their hyperactivity and be reluctant to give it up. For all the reasons just mentioned, one can anticipate problems with compliance.

Axis I comorbidity: Additional concerns

It appears that mood disorders, both unipolar and bipolar, substance abuse (particularly alcohol and cocaine), and attention deficit hyperactivity disorder play a significant role in the presentation of pathological gambling. While drug studies deliberately try to exclude these dually diagnosed patients in order to treat the “pure gambler,” the clinician in the field has no such option. In fact, medication is most often used to treat comorbidity. There is a precedent for this from the chemical dependency field. Studies have shown that cocaine abusers with coexisting major depression, attention deficit disorder, and bipolar disorder have done well when treated, respectively, with antidepressants, stimulant medications, and mood stabilizers (Weiss, Pope & Mirin, 1985; Gawin & Kleber, 1986; Ziednis & Kosten, 1991).

The key is proper diagnosis. Weiss and Collins (1992) have reviewed some of the problems this has posed for the chemical dependency field. Structured interviews, they note, have improved reliability of diagnosis, but even structured interviews have been subject to criticism. “Some studies of the test-retest reliability of these instruments have shown only moderate short-term and long-term concordance levels in their ability to diagnose lifetime psychiatric disorders (p. 97).” A particular difficulty has to do with a lack of agreement about the length of time an individual

has to be drug free before another psychiatric disorder can be diagnosed. Some authors, they observe, have suggested that alcoholics need two weeks of abstinence from drinking before a coexisting diagnosis of major depression can be made, whereas other researchers have recommended an abstinence period of three months before making the diagnosis. Pathological gamblers admitted to an inpatient facility following a binge or prolonged gambling can have psychiatric symptoms which mimic a large number of psychiatric disorders. There are no studies utilizing serial psychological testing or repeat interviews to guide us as to when we should be evaluating comorbid disorders.

In addition to assessing the existence of a comorbid disorder and, if present, whether it is primary or secondary, is the daunting task of untangling multiple disorders. As difficult as it can be to distinguish between bipolar disorder and ADHD, a very real possibility, especially in the multi-impulsive and often multiply addicted pathological gambler, is that both are present. Winokur, Coryell, Endicott & Akiskal (1993) found that adults with bipolar disorder reported much higher rates of childhood ADHD symptoms than did adults with unipolar depression. West, McElroy, Strakowski, Keck & McConville (1995) noted that 57% of patients with adolescent mania met criteria for comorbid ADHD. In a longitudinal study, Biederman et al. (1996) found that bipolar disorder was present at baseline for 11% of children with ADHD, and that another 12% met criteria four years later. This has led these authors to suggest that ADHD may be a risk factor for bipolar disorder. Since pathological gambling is associated with both bipolar disorder and ADHD, one should expect to see patients in which all three are diagnosed and need to be treated. This has not been mentioned in the literature on pathological gambling.

Axis II disorders

Prevalence rates for comorbid personality disorder in pathological gamblers vary from 25% to 93%. Blaszczynski and Steel (1998) administered the Personality Disorder Questionnaire-Revised to 82 treatment-seeking pathological gamblers (73% male, 27% female). They found that 76 (93%) met diagnostic criteria for at least one personality disorder. Multiple, overlapping diagnoses were the rule. The majority of the gamblers had cluster B personality disorders, with particularly high rates of borderline (70%), histrionic (66%), and narcissistic (57%) personality disorders. High levels of impulsivity and affective instability were found in the subjects with these diagnoses. The rate of antisocial personality disorder among the sample was 29%.

Kruedelbach and Walker (2000) examined male inpatient gamblers and found that 39% met criteria for a personality disorder. Of those, 67 of 79 (85%) had cluster B, 13% had cluster C, none had cluster A. Again, most of the patients had more than one Axis II disorder, although only five of 79 had a mixed cluster (for example, B and C). Most prominent was narcissistic personality disorder. Thirty-five percent

were so diagnosed, and an additional 53% were described as having significant narcissistic features. Ten percent met criteria for antisocial personality disorder. All subjects were evaluated by structured interview (SCID-II) during a five-day assessment period at the beginning of treatment.

Specker et al. (1996) conducted structured interviews on 40 pathological gamblers (25 female, 15 male) seeking outpatient treatment in Minnesota. Only 25% met criteria for a personality disorder (17.5% cluster C, 5% cluster B, 5% cluster A). Avoidant personality disorder was two and a half times more common than any other Axis II disorder. Noteworthy is the difference in demographics and type of gambling reflected in these last two studies. In the Specker et al. study, the majority of subjects were female and there was a preponderance of slot, video poker, and pull-tab gamblers, as compared to the more traditional male gamblers examined by Kruedelbach and Walker (2000). This conforms to Lesieur's (1988) subtyping of gamblers into action seekers and escape seekers, and the clinical impression that action-seeking male gamblers, who play traditional games (competitive, skill-based), are more likely cluster B (narcissistic, some antisocial) while escape-seeking female gamblers, who play luck-based, less directly competitive games, are more likely cluster C (avoidant, dependent). Gender differences are found across the personality disorders, with avoidant and dependent personalities being diagnosed more frequently in women, while narcissistic and antisocial personality disorders are more frequently diagnosed in men (Stone, 1993).

Gitlin's (1995) comprehensive review of the pharmacotherapy of personality disorders makes it clear that there are no medications for specific personality disorders. Instead, medication is used to treat symptom clusters within or across disorders. A model with great utility (Siever & Davis, 1991) proposes four dimensions or symptom clusters: cognitive/perceptual organization, impulsivity/aggression, affective instability, and anxiety/inhibition. Thus, a pathological gambler with a comorbid narcissistic personality disorder might be treated with an SSRI if mood lability, depression, and rejection sensitivity are dominant symptoms (affective instability), but with an atypical antipsychotic or mood stabilizer if there is prominent acting out behavior (impulsivity/aggression). Similarly, a patient with an avoidant or dependent personality might be treated with an SSRI for depression, social phobia, or panic disorder (anxiety/inhibition).

It is again important to note difficulties in diagnosis. Each of the three studies looking at the prevalence of personality disorders (Specker et al., 1996; Blaszczynski & Steel, 1998; Kruedelbach & Walker, 2000) involved pathological gamblers in or near the beginning of treatment. Although personality disorders are, by definition, chronic and enduring patterns of maladaptive behavior, several studies on substance dependence (Blume, 1989; Nace, 1989; Pettinati, 1990;

Pettinati, Jensen & Tracy, 1991) have noted their apparent instability over time. Pettinati and her colleagues (1991) reported that approximately 53% of substance abusers who were diagnosed with a personality disorder two weeks into treatment for substance abuse no longer met criteria for any Axis II disorder one year post-treatment. Serial evaluations of pathological gamblers at various points in treatment and in recovery are needed to see how the diagnosis of a personality disorder is affected.

Subtyping

In the long run, the most useful approach to the pharmacotherapy of pathological gambling will be one that does not view it as a homogeneous disorder, but instead tailors treatment to subgroups and patient characteristics. There have been a number of attempts to subtype pathological gamblers (Bergler, 1957; Moran, 1970; Livingston, 1974; Graham & Lowenfeld, 1986; McCormick & Taber, 1987; McCormick, 1987; Lesieur, 1988; Blaszczynski, McConaghy & Frankova, 1990; Gonzalez-Ibanez, Saldana, Jiminez Murcia & Vallejo, 1995; Blaszczynski, Steel & McConaghy, 1997; Rosenthal & Rugle, 1998; Kruedelbach & Walker, 2000; Blaszczynski, 2000). The one that has been most useful to clinicians has been Lesieur's (1988) division into action seekers and escape seekers (see also Lesieur & Blume, 1991b).

According to Lesieur (Lesieur & Rosenthal, 1993), escape seekers say they are gambling to achieve numbness and a sense of oblivion. They relate their gambling to relationship problems and the need to anesthetize painful affects. Dissociation while gambling may aid in their escape seeking. They are attracted to repetitive, even monotonous games, which they play alone. They tend not to take a strategic approach to gambling, do not play directly competitive games, and typically do not boast when they win. Escape seekers are more apt to be female and start gambling at a later age (after forming their adult identities) than their male counterparts. Their games of choice are slot and video poker machines, bingo and lotteries.

Action seekers, who are more likely to be male, look for big payoffs, play competitive, skill-oriented forms of gambling, and speak of the “action” or excitement of gambling. They have a need to impress others; GA refers to their “big shot” mentality. Gambling for them often begins with an early winning phase, and a memorable, early “big win.” Action seekers typically favor the traditional forms of gambling: cards and casino table games, sports betting and horse race wagering. They are more likely to “handicap,” “count cards,” or be “percentage players.” Action seekers begin gambling at an earlier age, often in pre-adolescence, and they have an earlier onset of problems than the escape seekers. Action seekers also have gambling careers of longer duration than those of escape seekers, whose careers tend to be telescoped. Lesieur's typology has obvious

similarities to the ones proposed by Cloninger (1983) and Babor et al. (1992) for alcoholics.

Several other approaches seem to support Lesieur's classification. McCormick (1987) describes two types of male gamblers, the “recurringly depressed” and the “chronically understimulated.” The latter is hyperactive, gregarious, and narcissistic, has a need to relieve boredom and a low frustration tolerance, and shows high novelty seeking. The recurringly depressed type often has a history of trauma. Gambling provides an escape from the depressed state. Blaszczynski et al. (1990) postulate three subtypes: boredom-prone, depressed, and a third “mixed” group.

Kruedelbach and Walker (2000) surveyed inpatient, predominantly male gamblers and described two categories based on gambling preference. Type I gamblers prefer card playing, race track wagering, sports betting, and stock market gambling. Type II gamblers prefer machine gambling. They found that type I gamblers began gambling at an earlier age, had a longer gambling career, and scored higher on narcissism/power, extroversion, and excitement seeking than the type II gamblers. The type II gamblers, on the other hand, were higher on seeking escape from negative emotions and dissociation while gambling than the type I gamblers. Kruedelbach and Walker's choice of names will remind the reader of Cloninger's (1983) distinction between early and late onset alcoholism, although unfortunately the names have been reversed. Cloninger used “type I” to represent late onset alcoholics, and “type II” for the early onset alcoholics. Other than the confusing nomenclature, there are many similarities.

Lending further support to this typology, Comings et al. (1996) found two types of female pathological gamblers. The women not carrying the abnormal D2 dopamine receptor gene tended to be late onset gamblers with depression. The women carrying the genetic predisposition for pathological gambling started gambling, and developing problems from gambling, at an early age. Depression was not a prominent feature. Further analysis is needed to determine what kind of gambling they prefer, and if they can be characterized as action seeking.

A different, more clinical typology was suggested by Rosenthal and Rugle (1998), who related dominant comorbid diagnosis and its associated features to the patient's style or pattern of gambling behavior. They looked at reasons and motives for gambling, what triggered gambling episodes, progression, treatment needs and prognosis. They considered 11 possible subtypes: ADHD, antisocial, bipolar, dependent-avoidant, depressive, masochistic, multi-impulsive, narcissistic, neurotic, obsessive-compulsive and reactive. They found that many of these categories could easily be recognized, with distinct patterns of gambling and very different clinical needs. They encountered problems with overlap, particularly in patients with multiple diagnoses and in those who could not be easily diagnosed.

Their findings were preliminary and a formal study still needs to be conducted.

Kim believes that, in evaluating naltrexone response, an attempt should be made to separate gamblers according to the frequency and intensity of their cravings (Kim et al., 2001a). This might yield up to four subgroups, defined by the presence of mild, moderate or severe cravings, or their absence altogether. Kim criticizes the naltrexone treatment studies that enrolled alcoholics regardless of the presence or absence of cravings. His point is well taken, and perhaps should be taken even further. The strength of gambling cravings may be an important prognostic factor, to be taken account of in all treatment matching and outcome studies.

Potentially useful are attempts to correlate specific clinical syndromes with deficits in various neurotransmitter systems. Among the more difficult to treat pathological gamblers, clinicians may encounter the following three subtypes:

The multi-compulsive

In addition to gambling, these patients may abuse drugs or eat or masturbate compulsively, or be addicted to sex. In other words, they engage in multiple compulsive or addictive behaviors. However, the defining characteristic of these individuals is that they do most activities to excess, whether it be dieting, exercising, buying shoes or sunglasses, playing golf, having a relationship. It is as if they have “no brakes,” which is how some of them have described it. One might infer that they have low levels of serotonin and would respond to an SSRI.

The sensation seeker

Not all pathological gamblers are high sensation-seekers, but when type of game is taken into account, such a subgroup exists. Casino and racetrack gamblers score higher on sensation seeking than the general population (Coventry & Brown, 1993). Video poker machine gamblers tend to be low sensation-seekers. The difference seems to conform to the distinction between competitive, skill-based games and forms of gambling that are noncompetitive and primarily involve luck (Adkins, Kruedelbach, Toohig & Rugle, 1988). When pathological gamblers are grouped together, the high sensation-seekers and the low sensation-seekers cancel each other out. Some of these high sensation-seekers may be categorized as “adrenalin junkies.” At its extreme are those who engage in danger seeking and compulsory, excitatory violence. Solursh (1988, 1989) found this to be quite common in Vietnam combat veterans with posttraumatic stress disorder; he named it “combat addiction.” Van der Kolk, Greenberg, Boyd & Krystal (1985) refer to it as an “addiction to trauma,” and postulate a model based on catecholamine depletion. Medications which raise levels of dopamine and norepinephrine, and which therefore might be expected to benefit this subgroup of gamblers, include the MAO inhibitors, venlafaxine and buproprion.

The apathetic gambler

These individuals may be gambling because they do not believe they have anything else in their lives. They lack goals and ambition, and are particularly difficult to treat. Their “amotivational syndrome” has been related to low levels of dopamine (Campbell & Duffy, 1997). Furthermore, it has been observed that for many pathological gamblers procrastination is a common and incapacitating symptom. While procrastination is a complex problem, apathy and lack of motivation are among the factors involved. Buproprion may be the medication of choice for this subgroup.

Comings et al. (1996) have implicated deficits in the dopaminergic system in pathological gamblers consistent with earlier findings in other impulse control disorders. Pathological gamblers, as compared to controls, were found to have a higher prevalence of the A1 allele of the DRD2 gene. This suggests a significant decrease in the number of dopamine D2 receptors, and is consistent with Bergh et al. (1997) finding a decrease in dopamine with increases in metabolites DOPAC and HVA in the cerebrospinal fluid of pathological gamblers. More recently, Comings et al. (2001) have shown that dopamine, serotonin and norepinephrine genes are about equally involved in pathological gambling. Other genes, yet to be tested, may also be involved in this complex, polygenic disorder. Genetic profiling may be of use in predicting drug response. Winsberg and Comings (1999) showed that alleles at the dopamine transporter gene (DAT1, SLC6A3) predicted methylphenidate response in children with ADHD, and Kim et al. (2000) reported that alleles at the serotonin gene (HTT, SLC6A4) significantly predicted response to serotonin reuptake inhibitors in individuals with depression. Genetic profiling may assist in the identification of genetic subtypes and, particularly when matched with clinical subtypes or syndromes, may result in far more effective decisions about medication.

Summary

For clinicians and researchers, an important factor in choice of medication has been the similarity between pathological gambling and other disorders. Most often, comparisons are made with substance dependence. Hollander (Hollander & Wong, 1995; Hollander & Benzaquen, 1996), on the other hand, places pathological gambling in an obsessive-compulsive spectrum, a group of disorders believed to share symptomatology, neurobiology, and treatment response with OCD. This assumption has led him to use clomipramine (Hollander et al., 1992) and fluvoxamine (Hollander, 1998; Hollander et al., 1998; Hollander et al., 2000) with pathological gamblers. A third treatment model is based on pathological gambling's categorization as a disorder of impulse control. Kim (1998) believes that, for this group of disorders, the primary problem is uncontrolled urges, and the pattern of

expression for those urges may dictate the descriptive diagnosis, although it is actually secondary. According to his formulation, resolution of the urges will bring about resolution of the rest of the behavioral symptoms. This led him to use naltrexone (Kim, 1998; Kim et al., 2001a) with pathological gamblers and to treat other impulse disorders. Still another approach is based on the clinical observation that pathological gamblers are often attempting to self-medicate depression or control changes in mood. Of the attempts to treat pathological gamblers with mood stabilizers, the earliest published account (Moskowitz, 1980) was with patients with bipolar disorder. McElroy et al. (1996) has even postulated that impulse control disorders are part of a bipolar spectrum.

Comorbidity between pathological gambling, bipolar disorder, and substance dependence (cocaine, alcohol), and the similarities between these disorders, suggests the possible relevance of kindling for pathological gambling. Such gambling is progressive, with an increase over time in its severity and the consequences from the behavior, with an associated increase in feelings of shame, guilt and depression. What has not been studied is whether the progressive course of pathological gambling includes an increase in withdrawal symptoms, affective instability, and the frequency and intensity of cravings, and whether external stressors play a progressively diminished role with seemingly autonomous episodes occurring later in the disorder. What are needed here are studies comparing gamblers from the early, middle, and later phases of the disorder. The presence of kindling would make a strong case for earlier and more aggressive use of medication, and for its long-term use to prevent future relapses.

Current approaches

Comorbidity is the clearest indication for using medication with pathological gamblers. They have high rates of depression, bipolar disorder, and attention deficit hyperactivity disorder. These may be severe or subtle (soft spectrum or subthreshold), and the affective disorders may be primary, secondary, or, in the case of depression, both. However, comorbid diagnoses can be difficult to make. Several disorders may be present, and there is little known about the interrelationships between pathological gambling and substance dependence, bipolar disorder, and the personality disorders. It is known that a gambling binge can mimic all the criteria for bipolar disorder, and that gamblers admitted to treatment can present not only with symptoms of withdrawal but with symptoms that can be confused with almost every psychiatric disorder. We do not know how long to wait before diagnosing a comorbid disorder. Research utilizing serial testing and repeat interviews is greatly needed. It is most helpful to observe the patient during periods of remission from gambling and to obtain an independent history from family members, but for the therapist faced with the dual diagnosis patient this is not always possible.

The presence and type of comorbid personality disorder has been found to vary with geographical region, accessibility of forms of gambling, and the point in treatment at which the gamblers were evaluated. Anecdotal clinical reports support study findings of predominantly cluster B personality disorders, especially narcissistic and antisocial, in the action-seeking, male gamblers, and cluster C personality disorders, especially avoidant and dependent, in the escape-seeking, female gamblers. However, there are no medications for specific personality disorders (Gitlin, 1995). Pharmacotherapy is aimed at symptom clusters within or across disorders. Therefore, a second indication for medicating pathological gamblers is to diminish or treat specific symptoms or traits, such as impulsivity, or target symptom clusters.

Pathological gamblers seem to have particular difficulty with feelings of shame, guilt, helplessness, and depression. Anger is often a secondary response. A third indication for medicating gamblers is to make these negative affects more tolerable. The SSRIs seem to accomplish this through a general dampening of affect; the patient feels less. However, a second mechanism involving some inhibition of associative pathways may also be involved, so that the patient feels as intently but reacts less. Pathological gamblers typically are trying to avoid feelings or situations they view as intolerable (Rosenthal & Rugle, 1994), and they believe that escape is possible. Gambling, of course, is one such method of escape. It is noteworthy that at GA meetings one rarely if ever hears about serenity. For alcoholics, the opposite is true; serenity is what they are primarily striving for in recovery. Perhaps gamblers do not think such a state of mind is possible, or perhaps for competitive, driven individuals, it represents complacency or defeat. However, clinicians have been impressed by the “serenity” demonstrated by patients on SSRIs. The patients say they are still aware of the negative situations in their lives, but are more tolerant of them.

Finally, a fourth indication for the medication of gamblers is to reduce urges or cravings to gamble. The research on naltrexone (Kim et al., 2001a) is most promising, particularly when the medication is reserved for those gamblers with moderate to severe cravings. To date, however, there is a paucity of research on gambling cravings. We do not know what percentage of gamblers presenting for treatment have had and continue to have frequent or intense cravings, nor do we know what the relationship is between cravings and gambling behavior. There is an assumption that the gambler's cravings are similar if not identical to those experienced by the alcohol or cocaine dependent patient. While Potenza (2001) finds some support for this, it is important to remember that even in the chemical dependency field cravings are a troublesome phenomenon, highly subjective and with no agreed upon method of measurement.

In summary, there are four current approaches to the pharmacotherapy of

pathological gambling. Medication is used to: (1) treat comorbidity, (2) target symptoms, traits or specific symptom clusters, (3) reduce negative affects, and (4) reduce cravings. Problems with compliance are significant, but are reduced when medications are used in conjunction with psychotherapy and other psychosocial approaches.

Future approaches

Although clinical trials usually view pathological gambling as a homogeneous disorder, future approaches will tailor treatment to subgroups and individual patient characteristics. Of the various attempts to subtype pathological gamblers, the most useful to date has been Lesieur's distinction between action seekers and escape seekers (Lesieur, 1988; Lesieur & Blume, 1991b). This distinction should be considered in evaluating treatment outcomes and in looking at clinical interventions. For example, naltrexone will probably have a more profound effect on high sensation-seeking action gamblers where the medication will block the excitement of gambling but may also potentially cause dysphoria or depression as well as greater problems with compliance.

One would also expect these two subgroups to differ with regard to comorbidity and predominant symptom clusters, symptoms and traits. Thus a study conducted in a part of the country which has primarily slot and video machine gamblers, pull-tabs and bingo, would draw a population requiring one type of clinical intervention, while a treatment program in a different geographical location, or in a particular setting such as a veteran's hospital, would attract a different type of gambler. The latter might have a preponderance of male gamblers who are card players, sports and racetrack bettors, and clinicians might, therefore, expect greater efficacy from medications which address aggression, hyperactivity, and impulsivity. In the former group one might anticipate better results from medications that target depression, rejection sensitivity, and social phobia.

The distinction between action seekers and escape seekers also has relevance in evaluating other kinds of treatment modalities. For example, escape-seeking, female gamblers often do not do well in male-dominated GA meetings, and have particular difficulty with the acceptance of powerlessness required in working the first step. They find nothing therapeutic in this, since they have felt powerless all their lives. They do much better in programs that emphasize self-assertion and empowerment, while the opposite may be true for the action-seeking, male gambler.

Other attempts at subtyping, with obvious clinical implications, are typologies based on comorbid diagnoses, severity of cravings, and attempts to match neurotransmitter deficits with specific clinical syndromes. To illustrate the latter, we described multi-compulsive, high sensation-seeking, and apathetic/unmotivated

subtypes. Such an approach may soon be combined with genetic profiling. Comings et al. (2001) found dopamine, serotonin, and norepinephrine to be about equally involved in pathological gambling. There are studies of other disorders; for example, ADHD (Winsberg & Comings, 1999) and major depression (Kim et al., 2000), demonstrating the usefulness of genetic profiling in predicting drug response for specific individuals and populations. The matching of genetic profiling with clinical subtypes may result in more effective decisions about medication, and may be a major step toward providing the best possible treatment for the individual patient.

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Article Categories:

- Research review

Keywords:

Key words:
pathological gambling
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pharmacotherapy
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treatment
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subtyping

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comorbidity
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cravings
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