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Pharmacological Treatment of Adolescent Pathological Gambling

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Introduction

Problem gambling among adolescents can be conceptualized as belonging to a larger constellation of "developmental addictions". Data support a relationship between "behavioral" and drug addictions in adolescents (Wagner & Anthony, 2002; Chambers & Potenza, 2003), and gambling, substance use, and other impulsive behaviors frequently co-occur in adolescents (Proimos et al., 1998; Romer, 2003). The co-aggregation of impulsive behaviors appears particularly frequent in adolescent males. Arguably the most consistent and robust finding across youth gambling studies is that boys are more involved in gambling than girls and have higher rates of problem gambling than do girls (e.g., Wallisch, 1993; Wynne Resources, 1996; Gupta & Derevensky, 1998; Stinchfield, 2001). Similarly, adolescent males have a greater likelihood of developing a substance use disorder than adolescent females. Nonetheless, the observation that these age-specific trends are observed in both males and females in epidemiological studies performed during different eras and involving different cultures suggests the existence of gender-independent factors in the developmental onset of addictive disorders (Chambers et al., 2003).

Research on developmental biology suggests that the adolescent brain is a changing organ and this has several important correlates. First, it suggests that treatments for adults might not work in the same manner in adolescents. Second, it suggests that treatments within adolescent groups might differ according to brain maturational stage, and that within subjects the effectiveness of specific treatments might vary over time. Third, treatments during specific developmental epochs in adolescence may have an enduring impact on the presence or manifestation of adult psychiatric syndromes. These points highlight the importance of studying directly the efficacy and tolerability of specific treatments in adolescents.

Adolescents as a group appear to constitute a high-risk population for gambling problems. While most adolescents gamble occasionally and do so responsibly, approximately 3% to 8% have been found to have a significant gambling problem (Shaffer and Hall, 1996; Derevensky and Gupta, 2000). Given the rates of adolescent problem gambling and its impact on affected individuals and their families, effective treatments are important. There are, however, no pharmacological treatments for pathological gambling in children, adolescents or adults that are currently approved by the Food and Drug Administration

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(FDA). Thus, it is important for patients, parents and guardians to understand that any use of medications for pathological gambling is off-label, and a review of the benefits and risks of pharmacotherapy and other treatment options is warranted in order to devise an appropriate treatment plan. No studies have investigated directly the safety and efficacy of pharmacological treatments for pathological gambling in adolescents. Therefore, we will review briefly the literature on effective treatments in adults, describe safety data for the use of these drugs in adolescents, and provide a rationale for future studies to investigate the efficacy and tolerability of pharmacotherapies for pathological gambling in adolescents.

Pharmacotherapy

The peer-reviewed literature indicates that pharmacological treatments have only been examined using randomized clinical trial methodologies in adults with pathological gambling, and, therefore, there is no direct evidence of either safety or efficacy of these treatments in adolescents with the disorder. Developmental issues are important to consider when prescribing medication for adolescents. Because adolescents may metabolize medications more rapdily than do adults, some adolescents may require higher doses relative to body weight compared to adults. On the other hand, because adolescents may have less adipose tissue than adults, there may be more bioactive drug available and therefore a greater likelihood of adverse events or a need for lower doses. Differences in central nervous system functioning and hormonal changes may further influence adolescents' responses to various medications.

Opioid Antagonists

Given their ability to modulate dopaminergic transmission in the mesolimbic pathway, opioid receptor antagonists have been investigated in the treatment of pathological gambling. There is evidence suggesting that naltrexone, a mu-opioid receptor antagonist, is effective in reducing gambling and gambling urges in adults with pathological gambling. An initial double-blind study suggested the efficacy of naltrexone, an FDA-approved treatment for alcohol dependence and opioid dependence, in reducing the intensity of urges to gamble, gambling thoughts and gambling behavior (Kim et al. 2001). In an 11-week, double-blind, placebo-controlled study of 45 subjects with pathological gambling, significant improvement was seen in 75% of naltrexone-treated subjects (mean dose 188mg/day) compared to 24% of those treated with placebo. In particular, individuals reporting higher intensity gambling urges responded preferentially to treatment (Kim et al. 2001).

Findings from the initial naltrexone study were recently replicated in a larger, longer study of 77 subjects randomized to either naltrexone or placebo over an 18-week period. Subjects assigned to naltrexone had significantly greater reductions in gambling urges and gambling behavior compared to those receiving placebo. Subjects assigned to naltrexone also had greater improvement in psychosocial functioning. By study endpoint, 39.7% of those on naltrexone were able to abstain from all gambling for at least one month, whereas only 10.5% pf those subjects receiving placebo attained complete abstinence for the same time period (Grant, Kim, Hartman, 2008).

Another opioid antagonist, nalmefene, has also shown promise in the treatment of pathological gambling. Nalmefene is currently not available in oral form in the United States. In a large, multi-center trial, using a double-blind, placebo-controlled, flexible-dose design, 207 subjects were assigned to receive either nalmefene at varying doses or placebo. At the end of the 16-week study, 59% of those assigned to nalmefene showed significant reductions in gambling urges, thoughts and behavior compared to only 34% receiving placebo (Grant et al. 2006).

Using data from nalmefene and naltrexone trials described above, analyses were performed to identify factors associated with a positive treatment outcome (Grant, Kim, Hollander & Potenza, 2008). Consistent with the influence of opiate antagonists on alcohol consumption, a familial history of alcoholism was associated with a positive treatment response as were strong gambling urges at treatment onset. In placebo-treated patients, younger age was the factor most closely associated with a positive placebo response. This finding, in conjunction with high placebo response rates observed in clinical trials involving adults with pathological gambling, suggests that placebo responses in adolescents with pathological gambling warrant consideration and that the findings from open-label trials be considered cautiously.

Naltrexone has been used in the treatment of autism and appears to be well tolerated in young patients (Campbell et al., 1993; Kolmen et al., 1995). Although not clearly beneficial for the social deficits of autism, naltrexone has demonstrated efficacy in controlling the hyperactivity of autistic children and adolescents (Campbell et al., 1993; Kolmen et al., 1995). Preliminary results in the treatment of alcoholic adolescents support the efficacy of naltrexone in promoting abstinence when combined with a supportive psychotherapy (Lifrak et al., 1997).

Naltrexone has demonstrated some efficacy in adolescents with autism and alcohol use disorders when used at 50mg/day. The findings from studies of adults with pathological gambling suggest that naltrexone may be a promising treatment for adolescents with the disorder. The safety of naltrexone at the higher doses used in the adult studies (up to 200 mg/day), however, has not been examined in an adolescent population. Doses of naltrexone greater than 50mg/day have warranted a “black box” warning due to the medication’s propensity for hepatotoxicity, particularly at higher doses (Physician’s Desk Reference, 2003). Therefore, more research on both the efficacy and safety of naltrexone in adolescent pathological gambling is needed to inform prescribing guidelines.

Antidepressants

Clomipramine

Serotonin reuptake inhibitors (SRIs), drugs blocking the action of the serotonin transporter and thus increasing synaptic availability of serotonin, have been used with varying degrees of success in treating adults with pathological gambling. Clomipramine, a relatively non-selective SRI, was administered in a double-blind, placebo-controlled trial of one female subject who reported a 90% improvement in gambling symptoms when treated with 125mg of clomipramine (Hollander et al. 1992). Gambling behavior remitted at week three of the trial and improvement was maintained for the next 7 weeks of the trial.

Clomipramine is currently FDA-approved for the treatment of obsessive-compulsive disorder (OCD) in adolescents. Three studies have found the medication safe and efficacious in treating adolescent OCD. In one double-blind study, a mean dose of 141 mg/d resulted in a significant decrease of OCD symptoms compared to placebo (Flament et al., 1985). A later study comparing clomipramine to desipramine found that a mean dose of 150mg/day resulted in a significantly greater improvement in OCD symptoms compared to desipramine (Leonard et al., 1989). A multicenter study of clomipramine further supported the efficacy and safety of clomipramine in the treatment of adolescent OCD (DeVeaugh-Geiss et al., 1992). The most common adverse effects observed in adolescents, including dry mouth, somnolence and dizziness, are comparable to those seen in adults. Adverse cardiac effects are possible and patients should be followed with blood levels and EKGs for safety purposes. These studies suggest that clomipramine may be safe for adolescents with pathological gambling, although its effectiveness for this indication needs further study.

Fluvoxamine

Fluvoxamine, a selective SRI (SSRI), has demonstrated mixed results in two placebo-controlled, double-blind studies of adults with pathological gambling, with one 16-week, crossover study supporting its efficacy at an average end-of-study dose of 207mg/day (Hollander et al. 2000), and a second six-month parallel-arm study with high rates of drop-out finding no significant difference in response to active or placebo drug (Blanco et al. 2002). Fluvoxamine was the first SSRI to gain FDA approval for the treatment of adolescent OCD. Both an open-label study (Apter et al., 1994) and a subsequent double-blind study (Riddle et al., 2001) have demonstrated that fluvoxamine at doses ranging from 50mg to 300mg/day is effective and generally safe in the treatment of adolescents with OCD.

Paroxetine

Two studies examining paroxetine in the treatment of adults with pathological gambling have been conducted, but the results have been mixed. The first 8-week study demonstrated significantly greater improvement for those individuals assigned to paroxetine compared to placebo (61% of subjects on paroxetine showed improvement versus only 23% on placebo) (Kim et al. 2002). A 16-week, multi-center study of paroxetine, however, failed to find a statistically significant difference between active drug and placebo, perhaps in part due to the high placebo response rate (48% to placebo, 59% to active drug) (Grant et al. 2003).

Although never formally tested in adolescents with pathological gambling, paroxetine has been studied in adolescents suffering from major depressive disorder and OCD. In a double-blind study of adolescent depression, paroxetine was both safe and efficacious at doses equivalent to those used in adults (20 – 40mg/day) (Keller et al., 2001). Other studies, however, have found paroxetine treatment in adolescents to be associated positively with suicidality (Abbott, 2003). As such, the off-label use of paroxetine in the treatment of adolescent pathological gambling should be carefully considered and closely monitored.

Sertraline

In a double-blind, 6-month, placebo-controlled trial using sertraline for pathological gambling in adults, a mean dosage of 95mg/day demonstrated no statistical advantage over placebo in a group of 60 pathological gamblers (Sáiz-Ruiz et al. 2005). Sertraline is FDA-approved for OCD in children and adolescents age 6–17 years, but has not been studied in adolescents with pathological gambling.

Escitalopram

Escitalopram was used in a 12-week, open label trial with an 8-week double-blind discontinuation phase for responders in 13 subjects with pathological gambling and co-occurring anxiety disorders (Grant and Potenza 2006). At the end of the open-label phase (mean dose 25.4mg/day), six subjects were considered responders, with concurrent decreases in gambling and anxiety severity observed. Gambling and anxiety improvement was maintained for those randomized to continue receiving active escitalopram while assignment to placebo was associated with a resumption of gambling and anxiety symptoms.

The FDA recently granted approval to escitalopram for the treatment of adolescent depression. Two double-blind studies found it safe and more efficacious than placebo in treating depression in adolescents aged 12–17 years (references??).

Bupropion

A recent study used bupropion in a 12-week, double-blind, placebo-controlled design in 39 adults with pathological gambling. When subjects with at last one post-randomization visit

were assessed, nearly 36% of bupropion subjects and 47% of placebo subjects were classified as responders. However, high treatment discontinuation rates of nearly 44% were observed in this study, thus making definitive statements difficult to make regarding the efficacy of bupropion in the treatment of adult pathological gambling (Black et al. 2007).

Response of adult gambling symptomatology to medications approved for depression and anxiety, particularly in the placebo-controlled trials of SSRIs, usually involves decreased thoughts about gambling, reductions in gambling, and improvement in social and educational or occupational functioning. Patients may initially report feeling less preoccupied with gambling and feeling less anxious about having thoughts of gambling. As these studies have often excluded individuals with significant depressive or anxious symptoms and changes in gambling behaviors and overall clinical status occur independently from changes in depression or anxiety, the data suggest that modulation of serotonin function in adults with pathological gambling may mediate improvement in symptoms specifically related to gambling.

Data supporting the efficacy of SRIs in the treatment of adult pathological gambling, albeit mixed, suggest that these medications may be beneficial in adolescents with pathological gambling. However, given changes during adolescence in serotonergic neuronal structure and function in such brain regions as the prefrontal cortex, direct investigation of the efficacies and tolerabilities of specific SRIs in adolescents with pathological gambling is warranted. The use of these medications in adolescents suffering from mood disorders or OCD suggests that many of these medications may be safe in adolescents with pathological gambling. These medications, however, carry a warning about the possible increase in suicidality in young people, and therefore should be used cautiously.

Mood Stabilizers

Lithium

Sustained-release lithium carbonate was used in a 10-week, double-blind, placebo-controlled study of 40 adults with bipolar spectrum disorders and pathological gambling. Lithium (mean level 0.87 meq/liter) was superior to placebo in reducing the thoughts and urges associated with pathological gambling. No significant differences between groups were found in the episodes of gambling per week, time spent per gambling episode, or the amount of money lost (Hollander et al. 2005b).

Lithium has been FDA-approved for the treatment of bipolar disorder in adolescents and has demonstrated safety in this population (Geller et al., 1998). Common adverse effects of lithium appear similar to those in adults: nausea, polyuria, tremor and acne.

Given its general safety profile in adolescents and its efficacy in treating adult pathological gambling, lithium may be a potentially useful treatment for adolescent pathological gambling. Studies of lithium in adolescents with pathological gambling are therefore needed.

Atypical Antipsychotics

Atypical antipsychotics, including drugs like risperidone, olanzapine, and ziprasidone, generally share the ability to antogonize serotonin $5HT_2$ and dopamine D_2-like (D_2, D_3, and D_4) receptors (Potenza & McDougle, 1998). These drugs have been explored as monotherapies and augmenting agents in the treatment of non-psychotic disorders and behaviors, including pathological gambling. Two recent studies have examined the use of olanzapine in the treatment of pathological gambling.

In a 12-week, double-blind, placebo-controlled trial of 42 adults with pathological gambling, olanzapine (mean dose 8.9 [5.2] mg) resulted in a 35% or greater reduction in PG-YBOCS (Yale-Brown Obsession and Compulsion Scale modified for Pathological Gambling) scores in 66.7% of the olanzapine group. However, 66.7% of the placebo group had the same reduction in PG-YBOCS scores. No statistically significant treatment effect was noted for olanzapine (McElroy et al. 2008).

In another study using olanzapine, Fong and colleagues (2008) tested 21 adults with pathological gambling in a 7-week, double-blind, placebo-controlled trial. All subjects reported their primary form of gambling as video poker. Reductions in cravings to gamble and gambling behavior were noted in both the olanzapine and placebo groups; however, no statistically significant differences between groups were observed.

Currently several atypical antipsychotic are FDA-approved for use in adolescents (e.g., schizophrenia, bipolar disorder, or autism). Although atypical antipsychotic drugs have been found to be well-tolerated in short-term trials involving adolescents (Stigler et al., 2001), increasing concerns have been raised regarding their adverse effect profile, particularly regarding their propensity for impaired glucose control and weight gain in adults and adolescents (Stigler et al, 2001). As such, emerging data regarding the long-term risk-benefit ratio may influence the decision to use these drugs in adolescents in general. Given the lack of support for the use of atypical antipsychotics in treating adults with pathological gambling and the potential risks of using these drugs with regard to such adverse effects as weight gain and impaired glucose regulation, their use in adolescents with pathological gambling would need to be well justified and carefully monitored over time.

Glutamatergic Agents

Because improving glutamatergic tone in the nucleus accumbens has been implicated in reducing the reward-seeking behavior in addictions (Kalivas, Peters, Knackstedt 2006), N-acetyl cysteine (NAC), a glutamate modulating agent, was administered to 27 adults with pathological gambling over an 8-week period with responders randomized to receive an additional 6-week double-blind trial of NAC or placebo. 59% of subjects in the open-label phase experienced significant reductions in pathological gambling symptoms and were classified as responders. At the end of the double-blind phase, 83% of those assigned to receive NAC were still classified as responders compared to only 28.6% of those assigned to placebo (Grant, Kim, Odlaug 2007). The only reported side effects included mild nausea or flatulence. In studies of marijuana dependence and autism in children and adolescents, similar doses of NAC have been examined with similar side effect profiles to that seen in adults.

Future Directions

Attention deficit hyperactivity disorder (ADHD) is among the most common mental illnesses in adolescents, with prevalence estimates in this population of 3–7% (Ford et al., 1999; Bloom et al., 2009). Adolescents suffering from ADHD often present with impulsivity and ADHD appears to confer a risk for the development of substance use disorders (Mannuzza et al., 1993; McGough et al., 2005; Molina et al., 2007). Interestingly, an early study found that 24% adults with pathological gambling suffered from co-occurring ADHD (Specker et al., 1995).

The high rate of comorbidity between pathological gambling and ADHD may suggest shared neuropathology. Evidence suggests that both pathological gambling and ADHD are associated with alterations in the function of the prefrontal cortex (PFC) and in the PFC's connections to the striatum and cerebellum (Brennan and Arnsten, 2008; Potenza et al.,

2003). The PFC is important for sustaining attention over a delay, inhibiting distraction, and allocating attention. The PFC in the right hemisphere, particularly in the right inferior frontal gyrus, may be especially important for behavioral inhibition (Chamberlain and Sahakian, 2007). Lesions to the PFC may produce a profile of distractibility, forgetfulness, impulsivity, poor planning, and locomotor hyperactivity.

Given the high rates of comorbidity and possible shared neuropathology between pathological gambing and ADHD, medications that enhance decision-making in ADHD may also benefit the impulsivity underlying the gambling behavior. A recent study compared the effects of stimulant medication on decision making in ADHD by examining performance on the Cambridge Gamble Task between boys with and without ADHD. In comparison with healthy control subjects, the ADHD group made poorer decisions, placed their bets more impulsively, and adjusted their bets less according to the chances of winning. The study found that the ADHD group bet more conservatively on the methylphenidate session than on the placebo session (DeVito et al., 2008). Based on this research, future pharmacological studies may wish to examine the effects of stimulant medication on adolescents with pathological gambling, particularly those with co-occurring ADHD. Future studies should also address the extent to which the observed ADHD findings extend to girls with the disorder and how the findings might then relate to the treatment of girls with pathological gambling.

Conclusion

Despite the high prevalence of pathological gambling in adolescents, research on this disorder, particularly with respect to pharmacological therapies, is in its relative infancy. Our understanding of neurodevelopmental changes that occur during adolescence, and their influence on adolescent behaviors, is at an early stage. Longitudinal studies involving neuroimaging, genetics, and behavioral assessments should help advance our understanding of adolescents, and with this understanding should come advances in prevention and treatment strategies for problems frequently experienced by adolescents, including risk behaviors such as pathological gambling.

Available data on pathological gambling in adults suggest several possible pharmacological interventions. At present, arguably the best evidence suggests the use of naltrexone and lithium in treating pathological gambling in adults. However, no data exist directly evaluating the efficacy and safety of pharmacological treatments for pathological gambling in adolescents. Pharmacological treatment of other disorders in adolescents suggests that certain medications - SRIs, mood stabilizers, naltrexone - appear safe and effective at certain doses and for certain indications. Although the data suggest potentially promising pharmacological treatments for adolescent pathological gambling, definitive treatment recommendations await completion of controlled treatment studies in this population. As the combination of behavioral and drug therapies has been demonstrated in other addictive disorders to be superior to either treatment alone (Carroll, 1997), future investigations in the treatment of pathological gambling in adolescents and adults should consider empirically validating such combined treatment approaches.

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