Substance Abuse in Schizophrenia: A Review

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Approximately half of the patients who suffer from schizophrenia are also substance abusers at some time during their illness. The motivational drive toward abusive consumption is compounded in individuals with schizophrenia who turn toward substances with reinforcing properties to alleviate aspects of psychosis. This review examines the prevalence, etiology, and clinical effects of substance abuse (e.g., alcohol, nicotine, cocaine) among individuals with schizophrenia. Clearly, substance abuse persists despite and in spite of treatment with typical antipsychotics. The efficacy of newer generation antipsychotics in the reduction of substance abuse among the schizophrenic population has yet to be established, but clozapine has been shown to reduce alcohol, smoking, and cocaine use. Hence, clozapine is a therapeutic option for dually diagnosed patients because of its superior efficacy relative to conventional neuroleptics and its capacity to control substance abuse. *(J Clin Psychiatry 1998;59[suppl 3]:26–30)*

PREVALENCE AND PRECIPITATING FACTORS

Substance abuse is strongly associated with mental illness. Over 50% of individuals who abuse drugs have severe and persistent mental illness.[1] Moreover, because the nosological complexities pose clinical difficulties in distinguishing drug-induced psychosis from "true" schizophrenia, individuals with schizophrenia and comorbid substance abuse are likely to be underrepresented and undertreated. These patients are notoriously difficult to effectively engage in treatment, and they have a reduced probability of therapeutic response with traditional antipsychotic drugs.[2]

What factors precipitate substance abuse among individuals with schizophrenia? In broad terms, it has been suggested that such patients may have an inherent vulnerability for developing schizophrenia when exposed to illicit drugs. Genetic vulnerability appears to be one contributing factor. Tsuang et al.[3] reported that familial background is an important factor affecting the duration of psychosis associated with substance abuse, suggesting overlapping biological mechanisms between psychosis and associated drug use. Consistent with the proposed genetic vulnerability, recent molecular genetic studies have shown that certain alleles of dopamine receptor subtypes are more common in frequent smokers.[4,5]

An alternative and clinically intuitive hypothesis is the "self-medication" hypothesis proposed by Khantzian.[6] It suggests that patients abuse drugs in an effort to alleviate the debilitating or intolerable chronic effects from psychiatric medications such as negative symptoms, neuroleptic dysphoria, extrapyramidal symptoms (EPS), or tardive dyskinesia (TD).[6,7] For example, schizophrenic patients experiencing neuroleptic dysphoria were found to be 4 times more likely to become substance abusers than patients without a history of neuroleptic dysphoria.[8] While typical antipsychotics control positive symptoms of schizophrenia, patients turn to alcohol and cocaine to alleviate the negative symptoms and dysphoria.[9] Moreover, accumulating evidence suggests that patients with schizophrenia who abuse alcohol or illicit drugs are at heightened risk of developing TD during exposure to conventional antipsychotics.[10]

DRUGS OF ABUSE

Clinicians should be cognizant of the prevalence and effects of readily available legal (e.g., caffeine, nicotine, alcohol, and over-the-counter pharmaceuticals) as well as illicit substances (e.g., marijuana, cocaine), particularly given that abuse of one drug class may reinforce abuse of other agents. I will explore in detail those commonly abused substances that are well represented in the literature—alcohol, nicotine, and cocaine. However, since schizophrenic patients invariably are polysubstance abusers, determining the relative effects of each involved substance in overall psychopathology and course of illness is difficult.

Alcohol

Alcohol abuse is prevalent in patients with mental disorders. Studies show that 45% to 60% of current and

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Supported by an unrestricted educational grant from Novartis Pharmaceuticals Corporation.

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Table 1. Clinical Effects of Substance Abuse in Schizophrenia

Earlier onset of schizophrenia
Psychotic relapse
Poorer functioning
Greater propensity for violence
Neuroleptic refractoriness
Noncompliance with medication
Tardive dyskinesia

former psychotic inpatients use alcohol primarily for its euphoric, antidepressant, or relaxing effects.[11–14]

In examining the chronology of substance abuse and schizophrenia, Hambrecht and Häfner[14] reported that alcohol abuse and drug abuse occurred before the onset of symptoms in 24% and 14%, respectively, of a first-episode sample of 232 schizophrenic patients. Alcohol abusers have been noted to have more florid symptoms, more rehospitalization, and a poorer long-term outcome.[13]

Nicotine

Whereas approximately one quarter of the U.S. population are smokers,[15] patients with schizophrenia have a disproportionately high incidence of smoking. Some reports cite that more than 70% of patients with chronic schizophrenia are nicotine dependent.[5,16] The extent of this problem is most evident in those patients with severe and persistent mental illness, especially those requiring long-term residential care.[17] Thus, the high proportion of smoking raises concern not only because of the harmful effects of cigarette smoke per se, but also because smoking may serve as a "gateway" to abuse of other substances.[5,16] However, the relationship between smoking and schizophrenia is complex, and the smoking may attenuate ill effects or neuroleptic effects, or both.

Patients with schizophrenia who smoke have demonstrated improvement in negative symptoms.[18] In addition, an analysis of auditory-evoked potentials suggests that nicotine improves the processing of auditory data in schizophrenic patients.[19] The elevated smoking rate among patients with schizophrenia may be due, in part, to heightened nicotine withdrawal symptoms that these patients can experience.[5]

Cocaine

Cocaine is a stimulant widely abused in society, particularly by persons with mental disorders. The lifetime prevalence for cocaine abuse among patients with schizophrenia is between 15% and 50%.[20,21] It has been suggested that some patients who abuse cocaine may actually have a less severe form of schizophrenia that is worsened by cocaine abuse. Cocaine abusers without a primary diagnosis of schizophrenia are likely to, in addition, have severe drug and alcohol abuse, addiction-related psychosocial impairment, antisocial behavior, and comorbid psychiatric problems.[22] It has also been reported that cocaine may reduce both positive and negative symptoms of schizophrenia and is often taken by psychiatric patients to relieve feelings of depression.[12]

CLINICAL EFFECTS OF SUBSTANCE ABUSE

Although substance abuse may provide acute relief from neuroleptic-induced side effects, such habituation has negative long-term effects on the management of schizophrenia (Table 1).

Substance abuse is associated with an earlier onset of schizophrenia and poor clinical function.[23] In 2 independent studies, heavy marijuana abuse was reported to precede the onset of psychotic symptoms by at least 1 year in 42% and 69% of the patients.[24,25] Another study found that drug abuse preceded (28%) or occurred within a month (35%) of the appearance of the first symptom of schizophrenia.[14]

D'Mello and colleagues[26] found that patients with schizophrenia who are substance-abusing tend to receive higher doses of antipsychotic medications. In a clinical trial of conventional antipsychotics in schizophrenic patients with and without a history of substance abuse, Bowers and colleagues[27] reported a poor treatment response in substance-abusing patients. They postulated that such neuroleptic refractoriness may be due to substance-induced alterations in mesolimbic dopaminergic systems.

Noncompliance with prescribed medication is a serious impediment to the effective treatment of schizophrenia and is even more problematic among patients with a dual diagnosis.[28] Owen and coworkers[28] noted that substance abusers with schizophrenia had no contact with healthcare providers, were noncompliant with medication, and had significantly greater symptom severity after 6 months. In another study of 42 schizophrenic inpatients, 57% admitted to drinking alcohol in the month before admission.[29] The majority of these patients (72%) were noncompliant with prescribed medication prior to hospital admission, and 62% of these patients reported being noncompliant specifically when drinking alcohol. Ironically, dually diagnosed patients may deliberately choose to be medically noncompliant, based on a treatment philosophy among drug abusers that espouses self-reliance, thereby precluding potential benefits of psychotropic medications. It is hardly surprising, then, that patients with schizophrenia who are substance abusers are predisposed to psychotic relapse. Gupta and colleagues[30] found that active substance abuse in such patients was highly related to readmission rates due to symptom recurrence. This finding was corroborated in a study by Swofford et al.,[31] which found that substance-abusing patients had 4 times more relapses of schizophrenia over 1 year than did nonabusing patients.[31] These findings accord well with clinical practice, although the complexity of this association, and possibly causation, between recent drug use and hospitalization is unclear but

Table 2. Factors That May Enhance the Therapeutic Efficacy of Clozapine and Other Novel Antipsychotics in the Treatment of Comorbid Substance Abuse in Schizophrenia

Low propensity for
extrapyramidal side effects
tardive dyskinesia
neuroleptic-induced dysphoria
Fewer negative symptoms
Altered mesolimbic dopaminergic tone (attenuation of craving?)
Selective antagonism of central serotonergic receptors (attenuation of craving?)
Psychosocial improvements may assist social skills
Increased medical monitoring may enhance therapeutic alliance
Weekly blood monitoring during clozapine therapy enables detection of noncompliance and relapse of substance abuse

is unlikely to be mediated solely by medication noncompliance.[32]

Recent studies have shown that alcohol can not only exacerbate psychosis but may also accelerate the appearance of TD.[33,34] Bailey and coworkers[35] examined 1027 patients with schizophrenia and found a very high correlation between substance abuse and diagnosis of TD. A comparative analysis of the prevalence of TD among 51 outpatients with schizophrenia (drug users and nonabusers) treated with antipsychotics revealed that weekly marijuana use was the best predictor for the appearance of TD.[36] Indeed, substance abuse may be an independent risk factor for movement disorders.[10]

REDUCTION OF SUBSTANCE ABUSE WITH NOVEL ANTIPSYCHOTICS

The enhanced efficacy of novel antipsychotics and their low propensity for EPS, in tandem with a potentially advantageous neurochemical profile, suggest that patients with schizophrenia who also abuse drugs may benefit preferentially from treatment with these agents.[37] Most evidence of this effect is based on experience with clozapine therapy and, thus far, there is insufficient information on the clinical efficacy of other atypical antipsychotics in this patient subgroup. Possible factors underlying this clinical advantage of clozapine and novel antipsychotics are highlighted in Table 2.

Marcus and Snyder[38] found that 85% of 13 schizophrenic smokers treated with clozapine reported either a reduction or cessation of smoking since taking clozapine. These patients did not attribute their decrease in smoking to a reduction in cigarette craving, but rather to an enhanced ability to plan and budget, to a concern over cost of cigarettes, or to a concern over health. These stated reasons reflect clozapine-related improvements in primary psychiatric symptoms. In another study that measured smoking rates in patients who changed from haloperidol to clozapine, smoking was decreased by 25% to 35% in patients with plasma clozapine levels greater than 200 ng/mL,[39] suggesting a direct drug-related effect on smoking.

Albanese et al.[40] reported case studies of patients with treatment-resistant schizophrenia who chronically abused alcohol. After clozapine administration, the patients exhibited a dramatic decrease in paranoia, became more sociable, and subsequently abstained from alcohol. In another study, Frankenburg[41] reported that 50% of schizophrenic patients with comorbid alcohol abuse had stopped drinking within 18 months after clozapine treatment.[2]

Preclinical and clinical data suggest that clozapine also reduces cocaine-seeking behavior. Kosten and Nestler[42] found that clozapine attenuates cocaine-conditioned place preference in rats. In addition, whereas low doses of typical antipsychotics increase stimulant self-administration, clozapine produces a dose-dependent decrease in cocaine intake in rats.[43] Vanover and colleagues[44] also noted a partial decrease in reinforcing and discriminative effects of cocaine in 50% of tested monkeys.

In one case study, decreased cocaine use after clozapine therapy was reported in a treatment-resistant 37-year-old man with schizoaffective disorder.[45] The patient demonstrated resolution of psychosis, improved social function, and a decreased need to use cocaine or other substances. There are other reports of dramatic cessation of substance abuse, attenuated craving, and improved psychosocial function during clozapine therapy.[37] In a study of substance abuse among patients with treatment-refractory schizophrenia, a comparable level of efficacy was observed in substance abusers and nonabusers after 6 months of clozapine treatment.[46] The results of this study indicate that the poor clinical response that is characteristic of drug-abusing schizophrenic patients may be improved with clozapine treatment. The data also suggest that a craving for illicit drugs may diminish with clozapine therapy.

There are, as yet, no published clinical trials on the efficacy of risperidone, olanzapine, or quetiapine in this patient population. Conley and colleagues[47] have recently presented data showing that olanzapine may be an effective treatment for patients with schizophrenia who have a history of substance abuse. Further studies of these novel antipsychotics in dual-diagnosis patients are warranted.

MECHANISM OF ACTION OF CLOZAPINE IN SUBSTANCE ABUSE

The pharmacologic mechanisms underlying the reduction in substance abuse during clozapine treatment are presently unresolved. However, such mechanisms presumably involve the mesolimbic dopamine system, which is associated with motivational states and is implicated in reinforcing the actions of most drugs of abuse.[48] Drugs with reinforcing properties (e.g., nicotine, alcohol, cocaine) increase extracellular dopamine levels in humans.[49] The decrease in smoking observed in schizophrenic patients taking clozapine, for example, may be due to its

ability to substitute for nicotine by augmenting dopamine release. Criswell and colleagues[50] reported that clozapine displayed both D_1 and D_2 receptor antagonism in rats hypersensitive to dopamine agonists. These researchers concluded that the greater affinity of clozapine for D_1 and lesser affinity for D_2, relative to typical antipsychotics, may play a role in modulating the activity of receptors involved in drug craving.

The therapeutic efficacy of clozapine is thought to derive not only from its unique pharmacologic profile but also from the totality of the treatment regimen. The mandatory visits for blood monitoring,[51] required primarily as a safety measure, have an auxiliary benefit of forming a therapeutic alliance between patient and healthcare professional.[37] This frequent contact also provides an important psychotherapeutic context to pharmacotherapy.

THE COST OF SUBSTANCE ABUSE IN SCHIZOPHRENIA: THERAPEUTIC IMPLICATIONS

Significant morbidity in the United States is attributed to mental illnesses and substance abuse, ranking third for personal healthcare expenditures.[52] Schizophrenia, in particular, is a major economic burden, with schizophrenia-related expenditures over $30 billion in the United States for both direct and indirect costs.[53] Comorbid substance abuse further increases the cost of care, because during periods of alcohol and/or illicit drug use, patients with schizophrenia become severely ill, resulting in symptoms that are more difficult to manage.[2] Schizophrenic patients who are substance abusers are frequent users of psychiatric and emergency services.[54] Moreover, dually diagnosed individuals are more likely to be unemployed and possibly homeless, drawing further on community service costs.[55] Also, some patients use disability payments to support their drug habits.[56] The lack of income to support the expense of drug abuse may be a precipitating factor leading some to crime and violence.

COST-EFFECTIVENESS OF CLOZAPINE

It is important that the economic disadvantages of comorbid substance abuse are highlighted and juxtaposed with current pharmacoeconomic perspectives on schizophrenia, particularly if it is asserted that novel antipsychotics should be used in this patient subgroup. Although more rigorous, prospective, pharmacoeconomic data are awaited, current evidence suggests that novel antipsychotics can, in spite of higher up-front prescription costs, save money in the long run.[53,57,58] Several studies attest to the cost-effectiveness of clozapine in treatment-refractory schizophrenia, particularly in the second year of therapy and thereafter. Meltzer and colleagues[59] have reported substantial cost savings attributable to clozapine therapy, mainly in reduced hospitalization. Of particular relevance to issues of treatment compliance and recidivism among substance abusers are the data showing substantial cost savings accrued when patients continued with clozapine therapy rather than discontinued. It has been argued that, in an era of resource allocation, resources should be focused on effective treatment for those patients who consume a disproportionate amount of health care dollars.[53,60]

CONCLUSIONS

Comorbid substance abuse in schizophrenia is a common and significant clinical dilemma. In many cases, substance abusers are noncompliant and therefore tend to be high users of emergency (and other) services, primarily because of psychotic relapse. Noncompliance and substance abuse are likely to be aggravated by patients' experience of neuroleptic-induced side effects such as EPS and neuroleptic dysphoria. Available evidence suggests that clozapine may reduce substance abuse among patients with schizophrenia. This potential benefit, allied with symptom reduction and improvement in overall psychosocial functioning, may result in a reduced risk of psychotic relapse and need for hospitalization, with consequent economic advantage. Additional studies are required to address these issues further, to explore the biochemical correlates of attenuated craving, and to determine whether these benefits also occur with other novel antipsychotics.

Drug names: clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

REFERENCES

1. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the epidemiologic catchment area (ECA) study. JAMA 1990;264:2511–2518
2. Young CR, Longhurst JG, Bowers MB Jr, et al. The expanding indications for clozapine. Exp Clin Psychopharmacol 1997;5(3):216–234
3. Tsuang MT, Simpson JC, Kronfol Z. Subtypes of drug abuse with psychosis: demographic characteristics, clinical features, and family history. Arch Gen Psychiatry 1982;39:141–147
4. Noble EP, St Jeor ST, Ritchie T, et al. D2 dopamine receptor gene and cigarette smoking: a reward gene? Med Hypotheses 1994;42:257–260
5. Ziedonis DM, George TP. Schizophrenia and nicotine use: report of a pilot smoking cessation program and review of neurobiological and clinical issues. Schizophr Bull 1997;23:247–254
6. Khantzian EJ. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. Am J Psychiatry 1985;142:1259–1264
7. Awad AG. Subjective response to neuroleptics in schizophrenia. Schizophr Bull 1993;19:609–618
8. Voruganti LN, Heslegrave RJ, Awad AG. Neuroleptic dysphoria may be the missing link between schizophrenia and substance abuse. J Nerv Ment Dis 1997;185(7):463–465
9. Brady K, Anton R, Ballenger JC, et al. Cocaine abuse among schizophrenic patients. Am J Psychiatry 1990;147:1164–1167
10. Lopez W, Jeste DV. Movement disorders and substance abuse. Psychiatr Serv 1997;48:634–636
11. Drake RE, Bartels SJ, Teague GB, et al. Treatment of substance abuse in severely mentally ill patients. J Nerv Ment Dis 1993;181(10):606–611
12. Dixon L, Haas G, Weiden PJ, et al. Drug abuse in schizophrenic patients: clinical correlates and reasons for use. Am J Psychiatry 1991;148:224–230
13. Drake RE, Osher FC, Wallach MA. Alcohol use and abuse in schizophrenia: a prospective community study. J Nerv Ment Dis 1989;177(7):408–414

14. Hambrecht M, Häfner H. Substance abuse and the onset of schizophrenia. Biol Psychiatry 1996;40:1155–1163
15. Hymowitz N, Jaffe FE, Gupta A, et al. Cigarette smoking among patients with mental retardation and mental illness. Psychiatr Serv 1997;48(1): 100–102
16. Kosten TR, Ziedonis DM. Substance abuse and schizophrenia: editors' introduction. Schizophr Bull 1997;23:181–186
17. De Leon J, Dadvand M, Canuso C, et al. Schizophrenia and smoking: an epidemiological survey in a state hospital. Am J Psychiatry 1995;152: 453–455
18. Ziedonis DM, Kosten TR, Glazer WM, et al. Nicotine dependence and schizophrenia. Hospital and Community Psychiatry 1994;45(3):204–206
19. Adler LE, Hoffer LD, Wiser A, et al. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. Am J Psychiatry 1993;150: 1856–1861
20. Schneier FR, Siris SG. A review of psychoactive substance use and abuse in schizophrenia: patterns of drug choice. J Nerv Ment Dis 1987;175(11): 641–652
21. Ziedonis D, Richardson T, Lee E, et al. Adjunctive desipramine in the treatment of cocaine abusing schizophrenics. Psychopharmacol Bull 1992;28: 309–314
22. Ball SA, Carroll KM, Babor TF, et al. Subtypes of cocaine abusers: support for a type A-type B distinction. J Consult Clin Psychol 1995;63(1): 115–124
23. Kovasznay B, Fleischer J, Tanenberg-Karant M. Substance use disorder and the early course of illness in schizophrenia and affective psychosis. Schizophr Bull 1997;23:195–201
24. Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry 1994;51: 273–279
25. Allebeck P, Adamsson C, Engström A. Cannabis and schizophrenia: a longitudinal study of cases treated in Stockholm County. Acta Psychiatr Scand 1993;88:21–24
26. D'Mello DA, Boltz MK, Msibi B. Relationship between concurrent substance abuse in psychiatric patients and neuroleptic dosage. Am J Drug Alcohol Abuse 1995;21(2):257–265
27. Bowers MB Jr, Mazure CM, Nelson JC, et al. Psychotogenic drug use and neuroleptic response. Schizophr Bull 1990;16:81–85
28. Owen RR, Fischer EP, Booth BM. Medication noncompliance and substance abuse among patients with schizophrenia. Psychiatr Serv 1996;47 (8):853–858
29. Pristach CA, Smith CM. Medication compliance and substance abuse among schizophrenic patients. Hospital and Community Psychiatry 1990;41(12):1345–1348
30. Gupta S, Hendricks S, Kenkel AM, et al. Relapse in schizophrenia: is there a relationship to substance abuse? Schizophr Res 1996;20:153–156
31. Swofford CD, Kasckow JW, Scheller-Gilkey G, et al. Substance use: a powerful predictor of relapse in schizophrenia. Schizophr Res 1996;20: 145–151
32. Richard ML, Liskow BI, Perry PJ. Recent psychostimulant use in hospitalized schizophrenics. J Clin Psychiatry 1985;46:79–83
33. Dixon L, Weiden PJ, Haas G, et al. Increased tardive dyskinesia in alcohol-abusing schizophrenic patients. Compr Psychiatry 1992;33(2):121–122
34. Olivera AA, Kiefer MW, Manley NK. Tardive dyskinesia in psychiatric patients with substance use disorders. Am J Drug Alcohol Abuse 1990;16 (1–2):57–66
35. Bailey L, Maxwell S, Brandabur MM. Substance abuse as a risk factor for tardive dyskinesia: a retrospective analysis of 1,027 patients. Psychopharmacol Bull 1997;33(1):177–181
36. Zaretsky A, Rector NA, Seeman MV, et al. Current cannabis use and tardive dyskinesia. Schizophr Res 1993;11:3–8
37. Buckley PF. Novel antipsychotic medications and the treatment of comorbid substance abuse in schizophrenia. J Subst Abuse Treat. In press
38. Marcus P, Snyder R. Reduction of comorbid substance abuse with clozapine [letter]. Am J Psychiatry 1995;152:959
39. McEvoy J, Freudenreich O, McGee M, et al. Clozapine decreases smoking in patients with chronic schizophrenia. Biol Psychiatry 1995;37:550–552
40. Albanese MJ, Khantzian EJ, Murphy SL. Decreased substance use in chronically psychotic patients treated with clozapine [letter]. Am J Psychiatry 1994;151:780–781
41. Frankenburg FR. Experience with clozapine in refractory psychotic illnesses. In: Standards of Care in Schizophrenia—Proceedings of a Consensus Conference. Sandoz Pharmaceutical Corporation; 1994:3–19
42. Kosten TR, Nestler EJ. Clozapine attenuates cocaine conditioned place preference. Life Sci 1994;55(1):PL9–14
43. Roberts DC, Vickers G. Atypical neuroleptics increase self-administration of cocaine: an evaluation of a behavioural screen for antipsychotic activity. Psychopharmacology (Berl) 1984;82:135–139
44. Vanover KE, Piercey MF, Woolverton WL. Evaluation of the reinforcing and discriminative stimulus effects of cocaine in combination with (+)–AJ 76 or clozapine. J Pharmacol Exp Ther 1993;266:780–789
45. Yovell Y, Opler LA. Clozapine reverses cocaine craving in a treatment-resistant mentally ill chemical abuser: a case report and a hypothesis. J Nerv Ment Dis 1994;182(10):591–592
46. Buckley P, Thompson PA, Way L, et al. Substance abuse and clozapine treatment. J Clin Psychiatry 1994;55(9, suppl B):114–116
47. Conley R, Gale E, Hirsch K. Olanzapine response in therapy-refractory schizophrenia with substance abuse (SA) [abstract]. Schizophr Res 1997; 24:190
48. Koob GF. Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol Sci 1992;13:177–184
49. Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 1988;85:5274–5278
50. Criswell HE, Mueller RA, Breese GA. Clozapine antagonism of D-1 and D-2 dopamine receptor-mediated behaviors. Eur J Pharmacol 1989;159: 141–147
51. Feldman J. Clozapine and agranulocytosis. Psychiatr Serv 1996;47(11): 1177–1178
52. Research on mental illness and addictive disorders: progress and prospects: a report of the Board on Mental Health and Behavioral Medicine, Institute of Medicine. Am J Psychiatry 1985;142(7 suppl):1–41
53. Buckley PF. Treatment of schizophrenia: let's talk dollars and sense. Am J Managed Care. In press
54. Bartels SJ, Teague GB, Drake RE, et al. Substance abuse in schizophrenia: service utilization and costs. J Nerv Ment Dis 1993;181(4):227–232
55. De Quardo JR, Carpenter CF, Tandon R. Patterns of substance abuse in schizophrenia: nature and significance. J Psychiatr Res 1994;28(3): 267–275
56. Shaner A, Eckman TA, Roberts LJ, et al. Disability income, cocaine use, and repeated hospitalization among schizophrenic cocaine abusers: a government-sponsored revolving door? N Engl J Med 1995;333:777–783
57. Hargreaves WA, Shumway M. Pharmacoeconomics of antipsychotic drug therapy. J Clin Psychiatry 1996;57(suppl 9):66–76
58. Honigfeld G, Patin J. A two-year clinical and economic follow-up of patients on clozapine. Hospital and Community Psychiatry 1990;41(8): 882–885
59. Meltzer HY, Cola P, Way L, et al. Cost effectiveness of clozapine in neuroleptic-resistant schizophrenia. Am J Psychiatry 1993;150:1630–1638
60. Davies LM, Drummond MF. Assessment of costs and benefits of drug therapy for treatment-resistant schizophrenia in the United Kingdom. Br J Psychiatry 1993;162:38–42