Drugs 2002; 62 (5): 743-755
0012-6667/02/0005-0743/$30.00/0

Substance Misuse in Patients with Schizophrenia

Epidemiology and Management

David J. Kavanagh,[1] *John McGrath,*[1,2] *John B. Saunders,*[1,3] *Glenys Dore*[4] and *Dianne Clark*[1]

1 Department of Psychiatry, School of Medicine, University of Queensland, Herston, Queensland, Australia
2 Queensland Centre for Schizophrenia Research, Wacol, Queensland, Australia
3 Alcohol and Drug Services of the Royal Brisbane Hospital and The Prince Charles Hospital Health Service Districts, Brisbane, Queensland, Australia
4 Macquarie Hospital and Department of Psychological Medicine, University of Sydney, North Ryde, New South Wales, Australia

Contents

Abstract

Substance misuse in individuals with schizophrenia is very common, especially in young men, in communities where use is frequent and in people receiving inpatient treatment. Problematic use occurs at very low intake levels, so that most affected people are not physically dependent (with the exception of nicotine). People with schizophrenia and substance misuse have poorer symptomatic and functional outcomes than those with schizophrenia alone. Unless there is routine screening, substance misuse is often missed in assessments. Service systems tend to be separated, with poor inter-communication, and affected patients are often excluded from services because of their comorbidity. However, effective management of these disorders requires a fully integrated approach because of the close inter-relationship of the disorders. Use of atypical antipsychotics may be especially important in this population because of growing evidence (especially on clozapine and risperidone) that nicotine smoking, alcohol misuse and possibly some other substance misuse is reduced. Several pharmacotherapies for substance misuse can be used safely in people with schizophrenia, but the evidence base is small and guidelines for their use are necessarily derived from experience in the general population.

1. Extent and Impact of the Problem

1.1 Incidence and Predictors

The second half of the 20th century saw both the deinstitutionalisation movement in Western psychiatry[1] and a substantial increase in the use of many psychoactive substances - a trend that has not yet peaked.[2] Comorbid substance use disorders in individuals with schizophrenia are now very common, with lifetime estimates in both the USA and Australia of over 40% (figure 1).[3-5] This represents a substantial increase in risk over the general population (4.6 times in the US Epidemiological Catchment Area study).[3] The rates in figure 1 exclude nicotine smoking, which in 1998 had a 12-month prevalence of 69% among Australians with psychosis (or 2.6 times the population rate).[5] Rates of misuse for specific substances are sensitive to community changes in substance use,[6] and therefore show variations between countries and over time. The substances that are currently the most commonly misused are nicotine, alcohol, marijuana (cannabis), followed by amphetamines in Australia,[5] and cocaine in the US.[6] In Australia, the number of people in the general community using injectable drugs has increased rapidly over recent years,[7-9] and this trend is also exhibited in people with schizophrenia.[5] Another recent phenomenon is a high rate of multiple drug use and misuse - for example, almost all marijuana users also use nicotine and/or alcohol.[5] Both alcohol and marijuana enhance the effects of nicotine, and mixing of nicotine and marijuana is common.

The likelihood of comorbidity is associated with the same factors as in the general community:

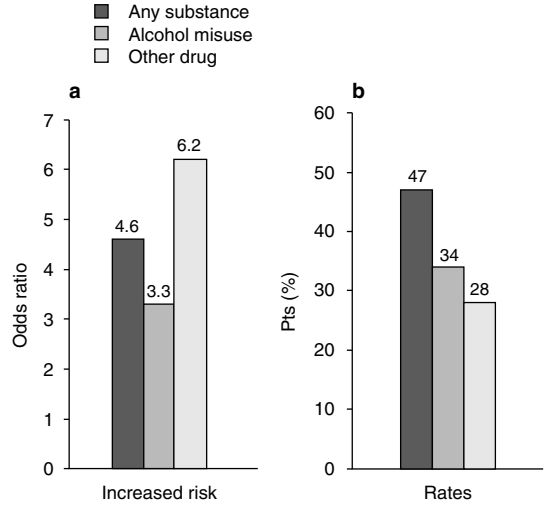

Fig. 1. Increased risk compared with the general population (**a**) and lifetime rates (**b**) of substance use disorders among people with schizophrenia in the Epidemiological Catchment Area Study.[3]

youth, male gender, unemployment, lower education, indigenous origin, and a history of antisocial personality, conduct disorder or family problems.[5,10,11] Rates are also higher within patients with psychosis receiving emergency or inpatient treatment.[12] The combination of these factors means that current substance misuse is seen in a majority of inpatients with early psychosis.[13]

Often patients with substance misuse show equal or better premorbid features and a wider range of current social contacts than those with schizophrenia alone.[11] Possible explanations include greater access to resources to pay for drugs, or an increased involvement in social activities where substance use occurs. In some contexts, a careful case-control study may even find that their substance use is not more severe or more common than for unaffected peers in their immediate subgroup.[14]

1.2 Effects of Substance Misuse

Substance misuse in schizophrenia is associated with an increased risk of illness and injury,[15] especially among women.[16] A major factor appears to be the accentuation of impulsivity and impaired cognitive functioning during intoxication, which increase the risk of accidents, victimisation, aggression and self-harm, as well as infection from sexually transmitted diseases including HIV. Some medical disorders are a direct result of the substance use. Although smokers with schizophrenia may have a lower incidence of respiratory cancers than other smokers,[17] recent work has indicated that people with schizophrenia have higher overall rates of smoking-related cancer than the general population,[18] simply because of the far higher prevalence of smoking amongst them.[5] Numerous other medical problems result from factors associated with substance use, such as poverty and homelessness.

Substance misuse is also linked to poorer outcomes from psychosis, and higher rates of presentation to inpatient and emergency services. Several substances, including psychostimulants, hallucinogens, marijuana and alcohol, trigger transient psychotic symptoms. Consumption during periods of vulnerability to psychosis can trigger relapse. Women who use substances may experience a greater relative impact on the course of schizophrenia than men.[19]

One reason for high relapse rates is a reduced rate of medication adherence and appointment attendance.[20] This has often discouraged prescribers from using clozapine in comorbid patients, because of the need for regular blood testing. In severely affected patients, a temptation is to place them on depot medications, which up to now has meant the use of traditional or 'typical' antipsychotics (with their more severe adverse effect profile and tendency to induce more substance misuse).

The effects of recreational substances interact with those of antipsychotic medication, and contribute both to the adverse effect profile and to noncompliance. For example, alcohol increases the sedation from antipsychotics and some patients deal with this by ceasing medication. Nicotine decreases serum typical antipsychotic concentrations by as much as 50%. The effective treatment dose is increased in smokers.[21] In one study, the average chlorpromazine equivalent daily dose was 375mg for nonsmokers and 590mg for smokers.[22] Although smoking can reduce extrapyramidal side effects (EPS) from antipsychotics in the short-term, on discontinuation of smoking the patient may have to deal with heightened EPS from both the higher dose and a reduction in dopaminergic activity. There is also an increased risk of tardive dyskinesia when patients use marijuana[23] or alcohol.[24]

Other common problems from substance misuse include unstable housing and homelessness, financial hardship, and loss of educational or employment opportunities. There are increased rates of criminal prosecution and incarceration, including for violent crime.[25] The financial and emotional burden on families is increased, and relationships may be lost.

These problems with substance misuse emerge at much lower levels of intake in people with

schizophrenia than in the general community,[26] because of their poor average baseline functioning and limited resources. For example, the purchase of a daily pack of cigarettes has a substantial impact on the budget of a patient on government benefits. Most affected people do not have high levels of physical dependence on substances other than nicotine and caffeine. In a recent study of inpatients with early psychosis,[13] an intake of just four cones of marijuana per week or any use of amphetamines was sufficient for problems to occur. The level of intake may often be the same or less than that of unaffected peers, rendering motivation to change consumption a significant challenge.

1.3 Reasons for an Increased Incidence in Schizophrenia

Explanations of increased rates of substance use in schizophrenia have been dominated by the self-medication hypothesis. While most users do not use substances to alleviate positive symptoms, they do often use them to deal with negative symptoms, sleeping problems, with dysphoria and other adverse effects of antipsychotic medication, including EPS.[27] Nicotine improves cognitive performance including selective attention[28] and habituation to repeated stimuli,[29] and reverses haloperidol-induced deficits in memory and complex reaction time,[30] as well as EPS problems mentioned in section 1.2. When the patient stops taking a substance, effects during withdrawal may be confused with the original reason for taking the drug, leading to resumption of use. In addition, clinical observation suggests that withdrawal discomfort from nicotine may be more severe or prolonged in individuals with schizophrenia than in the general population.

Recreational and social reasons for substance use are also important.[31] Drug use for pleasure can be seen as a socially normative variant of drug use to relieve dysphoria. However, a focus on recreational reasons highlights the importance of the leisure activity as well as pharmacological effects. Substance use is often a social event and, amongst those who are not psychotic, users may often be more accepting of odd behaviour and limited conversation than non-users. The number of substance users in the social network significantly predicts subsequent drug use.[32] This probably reflects acquaintance and activity selection as well as substance availability and social influence. People with schizophrenia often lack skills in social problem solving and drug refusal,[33] making them vulnerable to this social influence. Over time, social supports from family, friends and even health services are often withdrawn because of substance use,[32] rendering it even more difficult for the person to change consumption patterns.

2. Assessment

2.1 Self-Report

Given the high prevalence of substance use in people with schizophrenia, especially those in younger age groups, systematic enquiry should be made about the substance use of every patient with known or suspected schizophrenia. Presently this use is often missed or actively ignored, especially in relation to licit drugs[13] - a situation that can lead to inappropriate and ineffective treatment. Reasons include the failure of many patients to volunteer information because of embarrassment, fear of negative responses, cognitive impairment or lack of insight, and the low index of suspicion by clinicians. The presentation of substance misuse is often non-specific (e.g. anxiety, sleeplessness, dysphoria or restlessness) or may appear as a psychotic symptom (e.g. paranoia, hallucinations).

A good substance use assessment requires development of rapport and trust that a punitive response (e. g. rejection from the service or unpleasant treatment procedures) will not follow. When inquiring about intake, it is better to suggest higher levels of consumption, since this is less likely to lead to underestimation. The timeline follow-back method,[34] where events are used to assist recall of consumption, can usefully be adapted for patients with schizophrenia.

Systematic screening leads to substantially increased detection of comorbidity.[35] While some measures such as the Addiction Severity Index do

not perform well in comorbid populations,[36] others including the Alcohol Use Disorders Identification Test[37] and the Severity of Dependence Scale[13] show good reliability and validity in comorbidity, as do some screening measures especially designed for this population (e.g. the Dartmouth Assessment of Lifestyle Instrument[38] and DrugCheck[13]).

2.2 Biochemical Assays

Urine drug screening is a valuable diagnostic aid, and should be undertaken routinely when patients present with a psychotic disorder or develop an exacerbation of their symptoms. It should be undertaken without fail in admissions or patient reviews where the person is under the age of 40. Urine samples will show evidence of the parent drug, or one or more of its metabolites, if taken within 48 hours of the last use of the drug in most patients. Common substances and approximate detection periods are displayed in table I.

Nicotine is rapidly metabolised into cotinine, which has a half-life of about 15 hours in serum and saliva.[39] Moderate or regular cigarette smoking can be detected over longer periods within salivary thiocyanate (half-life 9.5 days).

Hair samples can be analysed for drugs and can give historical information about substance use over the previous weeks, and is well tolerated in patients with schizophrenia.[40] This may indicate use of a substance not reported by the patient or detected in periodic urine screens. However, hair analysis remains a research procedure in most regions. Other strategies include breath-analysis for alcohol or for carbon monoxide (CO) from cigarette smoking. Breath-analysis is limited by its relatively brief detection period (e.g. for expired CO, about 6 hours), but is useful for detection of very recent ingestion.[41]

2.3 Utility of Collateral Reports and Biochemical Assays

The presence of a substance screen tends to increase the accuracy of self-report - a phenomenon know as the 'bogus pipeline effect'.[42] Knowledge that collateral reports will be obtained can have a similar effect. Collateral reports of substance use by parents or other staff can be accurate independent sources of information when informants are in frequent contact with patients.[43] However, in practice neither biochemical assays nor collateral reports usually add to the accuracy of patients' self-reports,[43,44] as long as procedures are in place to maximise the accurate self-disclosure by the patient.

2.4 Potential for Diagnostic Uncertainty

When a person with substance misuse presents with psychotic symptoms, there are few differences in the acute symptoms between schizophrenia with substance misuse and substance-induced psychosis. The distinction is primarily made on the basis of a resolution of symptoms after withdrawal from the substance. For example, with a stimulant-

Table I. Urine screening for commonly misused substances in schizophrenia

Parent drug	Compound detected in urine	Internal half life of compound[a] (h)	Approximate reliable detection period[b]
Heroin	6-Monoacetyl morphine	2.2	48h
	Morphine	2.5	
Marijuana (cannabis)	11-nor THC	18-80	6wk
Cocaine	Benzoylecgonine	3	24h
Amphetamine and methamphetamine	Usually the parent compound predominates	15	48h

a The effective half-life in regular users may vary from these figures. For example, the release of stored THC from fat cells greatly increases the effective half-life in regular marijuana users.

b The reliable detection period is dependent on the amount of drug ingested and the sensitivity of the test method. These figures should be used as an approximate guide only.

THC = delta-9-tetrahydrocannabinol.

induced psychosis, the psychosis usually clears within days to a week of ceasing the stimulants.[45] Similarly, marijuana can cause a temporary psychotic state which usually clears within days or, at the most, several weeks. There is little difference in the treatment of acute symptoms between the two conditions, but substance-induced psychosis should not normally require maintenance on antipsychotic medication. However, it is important to keep in mind that some individuals with substance-induced psychosis may have a vulnerability to a less benign outcome in a future episode.

Non-response to medication should raise the questions on the potential role of substance use. Comorbid patients who are not responding to medication may not be taking it or their recreational substance use may be rendering it ineffective. Before changing pharmacotherapy, it is important to determine whether the symptoms resolve when adherence is assured and patients are not taking other substances.

3. An Overview of Intervention

3.1 Substance Use Goal and Motivational Enhancement

As in the general population, most people with schizophrenia would like to use at least some substances on a recreational basis. While we know that even a low substance intake may be problematic or unstable for many individuals,[46] engagement often requires some initial flexibility in treatment goal. This often means abstinence from the substances that the individual sees as most problematic, and a trial of reduced intake (with a contracted review point) on some other substances.

Nicotine smoking is often selected as an initial target, even though it may not be the greatest current problem and may prove particularly difficult to control (especially if marijuana or other substance use continues). In the general population, gradual scheduled reduction in smoking before a quit date is more successful than either 'cold turkey' quitting or unscheduled reduction.[47] Clinical experience suggests that gradual, scheduled reduction in smoking is both attractive and successful in comorbid populations, allowing the progressive development of skills.

It seems odd that some treatment services for comorbid populations require a period of sobriety before patients enter programs or require total sobriety during them. Such rules push the responsibility for engagement and success onto individuals and referral services, and do not display empathy for the difficulty even highly motivated patients have in attaining and maintaining control. As in the general population, people with schizophrenia and substance misuse often take several attempts before they successfully control substance use. We recognise that smokers may have five or more attempts before they permanently quit.[48] Clinical experience suggests that people with schizophrenia often have more. Clinical services should recognise this reality and reward intermediate success.

There is growing evidence that an adaptation of motivational enhancement[49] is effective in drawing patients into an attempt at substance control.[50] This approach is patient-centred but directive. It encourages patients to examine the benefits and costs of their substance misuse, answers questions or confirms correct beliefs about substance effects, and elicits dissonance between the substance use and other goals. Patients are encouraged to develop their own substance control and symptom management goals. Provided time is spent on developing trust and delivery is modified to accommodate thought disorder, this approach can even be applied with inpatients during an acute episode.[13] In fact acute episodes provide a window of opportunity for engagement because they offer compelling evidence of negative impact from substance use. At these and other times, financial cost and early signs of physical impact (in smoking - fitness, shortness of breath or respiratory infections) are other common motivators.

Many patients with good prognostic features and low intake or dependence require little treatment for substance misuse beyond this initial engagement.[13] Conversely if the person is not engaged and ready to change their substance use,[33]

other interventions may be mistimed and of little effect.

3.2 Integrated Service

Because schizophrenia and substance misuse are closely inter-dependent, parallel or sequential methods of treatment do not work as effectively as fully integrated treatment for both disorders.[51] However, this is inconsistent with the delivery systems for substance misuse and mental health disorders that have been established in many countries. Staff need to cross those practice boundaries when working with comorbid patients.

3.3 Psychological Interventions

Research on specific psychological strategies for substance use in this population is in its infancy. While 12-step approaches are commonly used for comorbid groups, they are unlikely to prove the most effective methods for many patients, because they do not involve an integrated approach to the disorders, have an inflexible goal, and sometimes oppose medication. Currently researchers are focusing on a range of strategies including family intervention,[52] problem solving, cognitive therapy,[53] development of substance refusal,[33] variations on community reinforcement strategies[54] to assist in development of lifestyle changes, and modifications of assertive community treatment programs.[55] Most of these psychological interventions appear broadly to be based on cognitive-behavioural procedures.[56,57] No single method has as yet emerged as most effective but elements of these procedures may prove useful with individual patients.

Our current opinion is that this psychological treatment should be titrated according to the patient's needs, so that at least some intervention can be widely available. At least three groups may be distinguished: those with mild substance-related problems who benefit from brief, motivational interventions; those who benefit from more extensive skills training and social support; and those with severe cognitive deficits who require ongoing environmental structure and social support for an indefinite period.[57]

4. Medication[1]

4.1 Management of Acute Psychotic Symptoms

The main focus of treatment for patients admitted to acute inpatient wards is rapid stabilisation of psychotic symptoms, hostility and agitation.[58] At the same time, longer-term goals need to be given consideration. These include minimising adverse effects, as these will impact on post-discharge compliance and quality of life.

Several 'atypical' antipsychotic medications have been introduced in recent years, including clozapine, risperidone, olanzapine, quetiapine and (in some countries) amisulpride and ziprasidone. These agents appear to be at least as effective as the typical antipsychotics for the treatment of positive symptoms,[59] and clozapine appears to have greater clinical efficacy, at least in patients who previously were treatment resistant.[60] Some other atypical antipsychotics have claimed statistically significant clinical advantages over typical antipsychotics, but it is unclear whether these differences are sufficient to be clinically relevant.[61]

However, there is robust evidence showing that the newer agents cause fewer EPS (e.g. parkinsonism, akathesia and acute dystonia) and a lower risk of tardive dyskinesia than typical antipsychotics.[62] Since patients who experienced EPS or neuroleptic dysphoria may use substances to alleviate these problems,[63] the newer agents may be of benefit to these patients. Whereas patients with comorbid substance misuse tend to have less negative symptoms than do other patients, in some the improved impact from atypical agents on negative symptoms may also be important in preventing the

1 A search of relevant bibliographic databases, including Medline and PsychInfo, was conducted for the years 1990 to 2001. Emphasis is placed on findings from randomised controlled trials where available. The principal finding from the literature search was the paucity of evidence on the management of comorbid schizophrenia and substance misuse.

use of nicotine or other substances to alleviate these symptoms.[64,65] Atypical antipsychotics are particularly important for those whose substance use puts them at increased risk of tardive dyskinesia.[27]

Patients on the newer agents also tend to have superior performance on neurocognitive measures (e.g. working memory) than do patients on traditional antipsychotic medications.[66,67] As a result, they may be more able to plan effective strategies to prevent substance misuse[68] and benefit more from psychological interventions,[69] although further research on this issue is required.

The net benefits of the new antipsychotics are such that patients should routinely receive a trial of an oral atypical antipsychotic. Most of the current data on comorbidity is based on clozapine, which shows approximately equal effectiveness in treatment-resistant patients with and without substance abuse.[70] However, concerns over the risk of agranulocytosis[71] may lead clinicians to begin acute treatment on other atypical antipsychotics such as risperidone or olanzapine.[58,72] The latter agents should be titrated to a therapeutic dose on day 1 or day 2 if possible. Appropriate doses are risperidone 4 to 6 mg/day and olanzapine 10 to 20 mg/day. Patients with suboptimal recoveries on these agents should then be given a trial on clozapine.

Of course, these agents are not themselves free of adverse effects. Clozapine and olanzapine have been associated with weight gain, which predisposes the individual to a wide range of later sequelae (e.g. diabetes mellitus, hypertension). The risk of agranulocytosis with treatment by clozapine requires that regular blood monitoring be undertaken.[71] Clozapine has also been linked to some cases of cardiomyopathy and fatal myocarditis,[73] rendering it advisable to monitor patients for myocarditis in the first month of treatment and for cardiomyopathy on a regular basis. As already noted in section 1.2, these monitoring requirements present a significant challenge for community management of some patients, especially where they frequently move location. Assertive contact strategies and multiple tracing methods will frequently be required for comorbid patients. Care should also be taken that adverse drug effects in people with comorbidity are not overlooked or misattributed to the recreational drug use.

Improvements from atypical medications should make them more effective in the management of comorbidity. While we currently lack controlled trials, there is emerging data that comorbid patients do have better substance use outcomes when receiving the newer antipsychotics. At present the best evidence is on reduced smoking when clozapine is prescribed,[74] but there is also some evidence for other antipsychotics[69] and for an impact of atypical agents on other drug use including alcohol and cocaine.[75,76] It is important to keep to the minimum effective dose if adverse effects are to be minimised and a reduction in recreational drugs obtained.

There are no controlled trials on specific medications that target symptoms produced by different substances. However, the likely transmitter/receptor mechanisms for those substance effects suggest drugs that might be optimally effective,[27] and we expect more targeted drugs before long.

4.2 Adjunctive Benzodiazepines

Adjunctive benzodiazepines should be used for breakthrough agitation and hostility in acute episodes, even where there is a history of substance abuse. The dose of benzodiazepine should take account of recent ingestion of other drugs and the prescription should be restricted to the short-term, with gradual dose reduction and withdrawal when the patient settles. At times, acutely agitated patients will require parenteral treatment with an antipsychotic or a benzodiazepine.

Benzodiazepines may also be required for detoxification from a number of substances, including alcohol, opiates, sometimes stimulants, and benzodiazepines themselves. Prescribing should be closely monitored and supervised, with limited amounts provided to outpatients, and care taken to avoid development of dependence.

4.3 Pharmacotherapies for Substance Misuse

Table II summarises the pharmacotherapies available for use in patients with comorbid substance misuse.

4.3.1 Nicotine Replacement

A standard regimen of nicotine replacement therapy (e.g. 21mg patch for 5 weeks, followed by 14mg and 7mg each for 2 weeks) appears to have some benefit in supporting attempts to quit smoking, without substantially increasing the risk of schizophrenic exacerbation.[69] Some patients require higher doses because of their high nicotine intake from smoking,[77] and the setting of dosage should take account of the smoking styles in comorbid patients which deliver high levels of nicotine per cigarette.[78] While there have been some case reports where psychosis developed during a quit attempt when patients were on nicotine patches,[79] small-scale group studies have not seen increased positive symptoms.[77] Nicotine withdrawal does not appear to induce psychotic symptoms, although it may induce distress.[80,81] Alternative explanations for these case reports include stress associated with the quit attempt or lapses into smoking after a quit period.

4.3.2 Bupropion

Although there are no reported randomised, controlled trials for the use of bupropion to reduce smoking in schizophrenia, there are some case reports[82] and non-blind studies that suggest it may be of benefit.[83] A recent case study[82] reported on a 41 year old man with chronic schizophrenia who had smoked three to five packs of cigarettes daily for 11 years. One week after receiving bupropion 150 mg/day, he reported he had lost the urge to smoke and stopped smoking entirely. Over 3 months, his clozapine dose was gradually reduced from 550 to 300 mg/day. His psychotic symptoms did not worsen and he obtained paid employment for the first time in 18 years.

Bupropion may, however, cause toxic effects in some people with schizophrenia. Bupropion has been found to cause seizures and psychosis at rates higher than other antidepressants.[84] It may induce psychosis by blocking dopamine uptake, causing dopaminergic overdrive. Lowering the dose or increasing the dose more slowly may alleviate a psychotic exacerbation.[85] Patients with a history of psychosis or mania will be more vulnerable to this problem and require closer monitoring. The risk of seizures is dose-related, and is increased by predisposing factors (history of previous seizures, eating disorders, alcohol dependence, unstable diabetes mellitus, head trauma, central nervous system tumour).[86]

Antipsychotics lower the seizure threshold and may make people with schizophrenia receiving bupropion more vulnerable to seizures. Accordingly, the Medicines Control Agency in the UK issued a message on 31 May 2001 regarding the use of bupropion in patients at risk of seizures (including patients receiving antipsychotics), stating that it '…must not be prescribed…unless there is compelling justification for which the potential benefit of smoking cessation outweighs the increased risk of seizure'.[87] They recommended that the treatment dose be reduced to 150mg per day in such situations. We also note that some clinicians are responding to this problem by prescribing adjunctive anticonvulsant medication, but are not aware of controlled trials supporting that practice.

Table II. Pharmacotherapies for comorbid substance misuse

Substance	Pharmacotherapies
Alcohol	Acamprosate
	Naltrexone
	Disulfiram *(second-line)*
Marijuana	*(nothing of proven benefit)*
Heroin and other opiates	Methadone maintenance
	Buprenorphine maintenance
	Naltrexone (*caution required)*
Tobacco	Nicotine replacement therapy
	Bupropion
Amphetamines	Antidepressants *(where persistent depression)*

4.3.3 Naltrexone and Acamprosate for Alcohol Dependence

Two valuable pharmacotherapies for alcohol dependence have been introduced into clinical practice in the past 2 to 5 years. They are naltrexone and acamprosate. Randomised controlled clinical trials have shown that both drugs increase the rate of abstinence (by approximately 2-fold) over 3 to 6 months (naltrexone) and 6 to 24 months (acamprosate). They also increase the percentage of abstinent days, reduce the risk of relapse into heavy drinking and reduce cumulative alcohol consumption. There are no controlled trials of acamprosate for alcohol dependence in patients with schizophrenia as yet, and naltrexone has not yet been shown to increase the effectiveness of alcohol treatment in patients with schizophrenia.[88] However, there do not appear to be any safety issues for their use in schizophrenia, and (pending further research) they may be worth considering with patients who have significant alcohol use disorders. Naltrexone has the advantage of once-daily dose administration, whereas acamprosate requires administration three times a day, which may be difficult in a poorly compliant group. Naltrexone will trigger rapid withdrawal from any regular opiate use and patients should appreciate the implications of naltrexone for emergency management of pain.

4.3.4 Disulfiram for Alcohol Dependence

Disulfiram is a longstanding treatment for alcohol dependence for which there is only moderate evidence of benefit.[89] There is case study evidence that disulfiram may assist with alcohol dependence in patients with schizophrenia,[90,91] and it seems that many patients can take it without an increase in positive symptoms.[91] The parameters for the use of disulfiram in patients with schizophrenia are similar to its use in patients with alcohol dependence alone.[92] Patients need to give informed consent to use the drug, be motivated to use the drug, not have an organic brain disorder, and not have a cardiac disorder that could be exacerbated by the alcohol-disulfiram reaction. Ideally, the disulfiram should be given under supervision (e.g. by a supportive relative).

There are reports that disulfiram may sometimes exacerbate or trigger psychotic symptoms at high doses.[93] This has been attributed to its ability to inhibit dopamine B-hydroxylase, leading to an accumulation of dopamine.[94] Although 250 mg/day does not appear to induce significant drug interactions or psychiatric complications in patients with alcohol dependence and psychiatric disorders,[95] close monitoring is desirable.

4.3.5 Opiate Dependence

Pharmacological treatments for opiate dependence are broadly classified into agonist (e.g. methadone or buprenorphine) or antagonist treatment (naltrexone). There are no controlled trials on the use of methadone for individuals with psychosis and opiate dependence. However, a substantial number of persons with schizophrenia undergo treatment with methadone maintenance without experiencing more than the usual incidence of adverse effects and clinical experience suggests that methadone is a useful treatment in comorbid patients. The patient needs to give informed consent for methadone treatment, be motivated to stop illicit opiate use and attend a clinic on a daily basis for treatment in initial stages. As with all patients commencing on methadone, the first 2 weeks (the 'stabilisation phase') is a crucial one. Patients with schizophrenia must be monitored closely for signs of toxicity, as there are some reports that methadone may alter antipsychotic requirements in patients with schizophrenia.[96,97] Withdrawal from methadone may trigger psychotic symptoms in some patients.[98]

In general, the starting dose of methadone should not exceed 20mg. This depends on the severity of dependence and degree of neuroadaptation. The dose should be increased by no more than 5mg per day, with a maximum daily dose at the end of the first week of 50mg. The ultimate dose for patients without psychiatric disorders is usually in the range of 60 to 120mg. There is no evidence for recommending a differential target dose in patients with schizophrenia. Prescribers should refer to more detailed guidelines published by their health authority.

4.3.6 Psychostimulant Dependence

There are no pharmacotherapies of proven worth for amphetamine or cocaine dependence, whether this is complicated by a psychiatric disorder or not.

5. Conclusion

At present, much of the management of comorbid substance misuse in patients with schizophrenia is based on a narrow evidence base that is influenced by research in the general population of substance use disorders or by research on the management of schizophrenia alone. However, the problem of comorbidity is receiving substantial current research attention, and improvements in both the psychological and pharmacological management are expected to develop quickly over the next 10 years.

References

1. Mercier C, Renaud C, King S. A thirty-year retrospective study of hospitalization among severely mentally ill patients. Can J Psychiatry 1994; 39 (2): 95-102
2. Australian Institute of Health andWelfare. 1998 National drug strategy household survey: first results. Canberra: Australian Institute of Health and Welfare, 1999
3. Regier D, Farmer M, Rae D, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 1990; 264 (19): 2511-8
4. Jablensky A, McGrath J, Herrman H, et al. Psychotic disorders in urban areas: an overview of the study on low prevalence disorders. Aust N Z J Psychiatry 2000; 34 (2): 221-36
5. Kavanagh DJ, McGrath JJ, Jenner L. Substance use in psychotic disorders: Results from the Australian survey of mental health and wellbeing [abstract]. Acta Psychiatr Scand 2000; 102 Suppl. 404: 5
6. Patkar AA, Alexander RC, Lundy A, et al. Changing patterns of illicit substance use among schizophrenic patients: 1984-1996. Am J Addict 1999; 8 (1): 65-71
7. Hall W, Ross J, Lynskey M, et al. How many dependent heroin users are there in Australia? Med J Aust 2000; 173 (10): 528-31
8. Maxwell JC. Changes in drug use in Australia and the United States: Results from the 1995 and 1998 National Household Surveys. Drug Alcohol Rev 2001; 20 (1): 37-48
9. Saunders JB, Richards A. Getting to grips with heroin and other opioid use. Med J Aust 2000; 173 (10): 509-10
10. Mueser KT, Yarnold PR, Rosenberg SD, et al. Substance use disorder in hospitalized severely mentally ill psychiatric patients: Prevalence, correlates, and subgroups. Schizophr Bull 2000; 26 (1): 179-92
11. Salyers MP, Mueser KT. Social functioning, psychopathology, and medication side effects in relation to substance use and abuse in schizophrenia. Schizophr Res 2001; 48 (1): 109-23
12. Mueser K, Yarnold P, Levinson D, et al. Prevalence of substance abuse in schizophrenia: demographic and clinical correlates. Schizophr Bull 1990; 16 (1): 31-55
13. Kavanagh DJ, Saunders JB, Young R, et al. Evaluation and brief intervention for substance abuse in early psychosis: A report to AUSEINET. Brisbane: Department of Psychiatry, University of Queensland; 1999
14. Condren RM, O'Connor J, Browne R. Prevalence and patterns of substance misuse in schizophrenia: A catchment area case-control study. Psychiatr Bull 2001; 25 (1): 17-20
15. Dickey B, Azeni H, Weiss R, et al. Schizoprhenia, substance use disorders and medical co-morbidity. J Ment Health Policy Econ 2000; 3 (1): 27-33
16. Brunette M, Drake R. Gender differences in patients with schizophrenia and substance abuse. Compr Psychiatry 1997; 38 (2): 109-16
17. Hoffer A, Foster HD. Why schizophrenics smoke but have a lower incidence of lung cancer: Implications for the treatment of both disorders. J Orthomol Med 2000; 15: 141-4
18. Lichtermann D, Ekelund J, Pokkala E, et al. Incidence of cancer among persons with schizophrenia and their relatives. Arch Gen Psychiatry 2001; 58: 573-8
19. Gearon JS, Bellack AS. Sex differences in illness presentation, course and level of functioning in substance-abusing schizoprhenia patients. Schizophr Res 2000; 43 (1): 65-70
20. Owen RR, Fischer EP, Booth BM, et al. Medication noncompliance and susbtance abuse among patients with schizophrenia. Psychiatr Serv 1996; 47 (8): 853-8
21. Goff D, Henderson D, Amico E. Cigarette smoking in schizophrenia: relationship to psychopathology and medication side effects. Am J Psychiatry 1992; 149 (9): 1189-94
22. Ziedonis D, Kosten T, Glazer W, et al. Nicotine dependence and schizophrenia. Hosp Community Psychiatry 1994; 45: 204-6
23. Zaretsky A, Rector N, Seeman M, et al. Current cannabis use and tardive dyskinesia. Schizophr Res 1993; 11: 3-8
24. Dixon L, Weiden P, Haas G, et al. Increased tardive dyskinesia in alcohol-abusing schizophrenic patients. Compr Psychiatry 1992; 33: 121-2
25. Raesaenen P, Tiihonen J, Isohanni M, et al. Schizophrenia, alcohol abuse, and violent behavior: A 26-year follow-up study of an unselected birth cohort. Schizophr Bull 1998; 24 (3): 437-41
26. Drake R, Osher F, Wallach M. Alcohol use and abuse in schizophrenia: A prospective community study. J Nerv Ment Dis 1989; 177: 408-14
27. Krystal JH, D'Souza DC, Madonick S, et al. Toward a rational pharmacotherapy of comorbid substance abuse in schizophrenic patients. Schizophr Res 1999; 35 Suppl. 6: S35-49
28. Adler LE, Hoffer LD, Wiser A, et al. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. Am J Psychiatry 1993; 150 (12): 1856-61
29. Kumari V, Toone B, Gray JA. Habituation and prepulse inhibition of the acoustic startle reflex: Effects of smoking status and psychosis-proneness. Pers Indiv Diff 1997; 23 (2): 183-91
30. Levin ED, Wilson W, Rose JE, et al. Nicotine-haloperidol interactions and cognitive performance in schizophrenia. Neuropsychopharmacology 1996; 15 (5): 429-36
31. Dixon L, Haas G, Weiden PJ, et al. Drug abuse in schizophrenic patients: clinical correlates and reasons for use. Am J Psychiatry 1991; 148 (2): 224-30
32. Trumbetta SL, Mueser KT, Quimby E, et al. Social netowrks and clinical outcomes of dually diagnosed homeless persons. Behav Ther 1999; 30: 407-30

33. Bellack AS, DiClimente CC. Treating substance abuse among patients with schizophrenia. Psychiatr Serv 1999; 50 (1): 75-80
34. Sobell LC, Sobell MB. Alcohol timeline followback users' manual. Toronto: Addiction Research Foundation, 1995
35. Appleby L, Dyson V, Luchins D, et al. The impact of substance use screening on a public psychiatric inpatient population. Psychiatr Serv 1997; 48: 1311-6
36. Carey K, Correia C, Cocco K. Reliability and validity of the addiction severity index among outpatients with severe mental illness. Psychol Assess 1997; 9 (4): 422-8
37. Seinen A, Dawe S, Kavanagh DJ, et al. An examination of the utility of the AUDIT in people diagnosed with schizophrenia. J Stud Alcohol 2000; 61: 744-50
38. Rosenberg SD, Drake RE, Wolfoprd GL, et al. Dartmouth Assessment of Lifestyle Instrument (DALI): a substance use disorder screen for people with severe mental ilness. Am J Psychiatry 1998; 155 (2): 232-8
39. Zevin S, Jacob-III P, Geppetti P, et al. Clinical pharmacology of oral cotinine. Drug Alcohol Depend 2000; 60 (1): 13-8
40. McPhillips MA, Kelly FJ, Barnes TR, et al. Detecting comorbid substance misuse among people with schizophrenia in the community: a study comparing the results of questionnaires with analysis of hair and urine. Schizophr Res 1997; 25 (2): 141-8
41. Waage H, Sisland T, Urdal P, et al. Discrimination of smoking status by thiocyanate and cotinine in serum, and carbon monoxide in expired air. Int J Epidemiol 1992; 21 (3): 488-93
42. Aguinis H, Pierce CA, Quigley BM. Enhancing the validity of self-reported alcohol and marijuana consumption using a bogus pipeline procedure: A meta-analytic review. Basic Appl Soc Psychol 1995; 16 (4): 515-27
43. Carey KB, Simons J. Utility of collateral information in assessing substance use among psychiatric outpatients. J Subst Abuse 2000; 11 (2): 139-47
44. Rankin H. Validity of self-reports in clinical settings. Behav Assess 1990; 12 (1): 107-16
45. Schuckit M. Drug and Alcohol Abuse. A Clinical Guide to Diagnosis and Treatment. New York: Kluwer Academic/Plenum, 2000
46. Drake R, Wallach M. Moderate drinking among people with severe mental illness. Hosp Community Psychiatry 1993; 44 (8): 780-5
47. Cinciripini PM, Lapitsky L, Seay S, et al. The effects of smoking schedules on cessation outcome: Can we improve on common methods of gradual and abrupt nicotine withdrawal? J Consult Clin Psychol 1995; 63 (3): 388-99
48. US Department of Health and Human Services. National trends in smoking cessation, in the health benefits of smoking cessation: a report of the Surgeon General. Washington: US Govt Printing Office, 1994
49. Miller W, Rollnick S. Motivational interviewing: preparing people to change addictive behaviour. New York: Guilford, 1991
50. Swanson AJ, Pantalon MV, Cohen KR. Motivational interviewing and treatment adherence among psychiatric and dually diagnosed patients. J Nerv Ment Dis 1999; 187 (10): 630-5
51. Drake R, Mercer-McFadden C, Mueser K, et al. Review of integrated mental health and substance abuse treatment for patients with dual disorders. Schizophr Bull 1998; 24 (4): 589-608
52. Kavanagh DJ, White A, Young R, et al. Towards an Integrated and Sensitive Family Intervention for Comorbid Substance Abuse and Schizophrenia: A Comment on Sheils and Rolfe (2000). Aust J Fam Ther 2000; 21: 88-90
53. Graham H. The role of dysfunctional beliefs in individuals who experience psychosis and use substances: implications for cognitive therapy and medication adherence. Behav Cog Psychother 1998; 26: 193-208
54. Hunt GM, Azrin NH. A community-reinforcement approach to alcoholism. Behav Res Ther 1973; 11 (1): 91-104
55. Drake RE, McHugo GJ, Clark RE, et al. Assertive community treatment for patients with co-occurring severe mental illness and substance use disorder: A clinical trial. Am J Orthopsychiatry 1998; 68 (2): 201-15
56. Kavanagh D. An intervention for substance abuse in Schizophrenia. Behav Change 1995; 12 (1): 20-30
57. Kavanagh DJ, Young R, Boyce L, et al. Substance abuse treatment options for schizophrenia (STOP): a new intervention for dual diagnosis. J Ment Health 1998; 7 (2): 135-43
58. Feifel D. Rationale and guidelines for the inpatient treatment of acute psychosis. J Clin Psychiatry 2000; 61 Suppl. 14: 27-32
59. Leucht S, Pitschel-Walz G, Abraham D, et al. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. Schizophr Res 1999; 35 (1): 51-68
60. Wahlbeck K, Cheine M, Essali A, et al. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. Am J Psychiatry 1999; 156 (7): 990-9
61. Emsley RA. Role of neweer atypical antipsychotics in the management of treatment-resistant schizophrenia. CNS Drugs 2000; 13 (6): 409-20
62. Casey DE. Tardive dyskinesia and atypical antipsychotic drugs. Schizophr Res 1999; 35: S61-6
63. Voruganti LNP, Heslegrave RJ, Awad AG. Neuroleptic dysphoria may be the missing link between schizophrenia and substance abuse. J Nerv Ment Dis 1997; 185 (7): 463-5
64. Rosenheck R, Dunn L, Peszke M, et al. Impact of clozapine on negative symptoms and on the deficit syndrome in refractory schizophrenia. Am J Psychiatry 1999; 156 (1): 88-93
65. Tollefson GD, Sanger TM. Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. Am J Psychiatry 1997; 154 (4): 466-74
66. Green MF, Marshall BD, Wirshing WC, et al. Does risperidone improve verbal working memory in treatment-resistant schizophrenia? Am J Psychiatry 1997; 154: 799-804
67. Hagger C, Bucley P, Kenny JT, et al. Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. Biol Psychiatry 1993; 34: 702-12
68. Marcus P, Snyder R. Reduction of comorbid substance abuse with clozapine [letter]. Am J Psychiatry 1995; 152: 959
69. George TP, Zeidonis DM, Feingold A, et al. Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. Am J Psychiatry 2000; 157: 1835-42
70. Buckley P, Thompson P, Way L, et al. Substance abuse among patients with treatment-resistant schizophrenia: characteristics and implications for clozapine therapy. Am J Psychiatry 1994; 151 (3): 385-9
71. McGrath J, Emmerson WB. Fortnightly review. Treatment of schizophrenia. BMJ 1999; 319 (7216): 1045-8
72. Currier G. Atypical antipsychotic medications in the psychiatric emergency service. J Clin Psychiatry 2000; 61 Suppl. 14: 21-6
73. Degner D, Bleich S, Grohmann R, et al. Myocarditis associated with clozapine treatment [letter]. Aust N Z J Psychiatry 2000; 34 (5): 880

74. McEvoy JP, Freudenrsich O, Wilson WH. Smoking and therapeutic response to clozapine in patients with schizophrenia. Biol Psychiatry 1999; 46: 125-9
75. Drake RE, Xie H, McHugo GJ, et al. The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. Schizophr Bull 2000; 26 (2): 441-9
76. Zimmet SV, Strous RD, Burgess ES, et al. Effect of clozapine on substance use in patients with schizophrenia and schizoaffective disorder: A retrospective study. J Clin Psychopharmacol 2000; 20 (1): 94-8
77. Addington J. Group treatment for smoking cessation among persons with schizophrenia. Psychiatr Serv 1998; 49 (7): 925-8
78. Lohr JB, Flynn K. Smoking and schizophrenia. Schizophr Res 1992; 8: 93-102
79. Scurlock H, Lucas P. Another case of nicotine psychosis? Addiction 1996; 91 (9): 1388
80. Dalack GW, Becks L, Hill E, et al. Nicotine withdrawal and psychiatric symptoms in cigarette smokers with schizophrenia. Neuropsychopharmacology 1999; 21 (2): 195-202
81. Smith CM, Pristach CA, Cartagena M. Obligatory cessation of smoking by psychiatric inpatients. Psychiatr Serv 1999; 50 (1): 91-4
82. Evins AE, Tisdale T. Bupropion and Smoking Cessation. Am J Psychiatry 1999; 156 (5): 798-9
83. Weiner E, Ball MP, Summerfelt A, et al. Effects of sustained-release bupropion and supportive group therapy on cigarette consumption in patients with schizophrenia. Am J Psychiatry 2001; 158 (4): 635-7
84. Howard WT, Warnock JK. Howard WT, et al. Bupropion-Induced Psychosis [letter]. Am J Psychiatry 1999; 156 (12): 2017-8
85. Golden RN, James SP, Sherer MA, et al. Psychoses associated with bupropion treatment. Am J Psychiatry 1985; 142 (12): 1459-62
86. Steele C. Zyban: an effective treatment for nicotine addiction. Hosp Med 2000; 61: 785-8
87. Breckenridge A. Zyban: modified dosage and safety precautions. Message from Professor A. Breckenridge, Chairman, Committee on Safety of Medicines, Medicines Control Agency. Available from URL: http://www.mca.gov.uk (safety messages) [Accessed 2001 May 31]
88. Sernyak MJ, Glazer WM, Heninger GR, et al. Naltrexone augmentation of neuroleptics in schizophrenia. J Clin Psychopharmacol 1998; 18: 248-51
89. Hughes J, Cook C. The efficacy of disulfiram: A review of outcome studies. Addiction 1997; 92 (4): 381-95
90. Brenner LM, Karper LP, Krystal JH. Short-term use of disulfiram with clozapine. J Clin Psychopharmacol 1994; 14: 213-5
91. Mueser KT, Noordsy DL, Fox L, et al. Disulfiram treatment for alcoholism in severe mental illness. Am J Addict. In press
92. Wetzler S, Sanderson WC. Treatment Strategies for Patients with Psychiatric Comorbidity. New York: John Wiley and Sons, 1997
93. Poulsen E, Loft S, Anderson JR, et al. Disulfiram therapy--adverse drug reactions and interactions. Acta Psychiatr Scand 1992; 86: 59-66
94. Perry PJ, Alexander B, Liskow BI. Psychotropic drug handbook. 7th ed. Washington (DC): American Psychiatric Press, Inc., 1997
95. Larson EW, Olincy A, Rummans TA, et al. Disulfiram treatment of patients with both alcohol dependence and other psychiatric disorders: A review. Alcohol Clin Exper Res 1992; 16 (1): 125-30
96. McKenna GJ. Methadone and Opiate Drugs: Psychotropic Effect and Self-Medication. Ann N Y Acad Sci 1982; 398: 44-53
97. Vereby K, Volavka J, Clouet D. Endorphines in psychiatry: An overview and a hypothesis. Archives Gen Psychiatry 1978; 35: 877-88
98. Levinson I, Galynker II, Rosenthal RN. Methadone withdrawal psychosis. J Clin Psychiatry 1995; 56 (2): 73-6

Correspondence and offprints: Dr *David J. Kavanagh*, Department of Psychiatry, University of Queensland, Mental Health Centre, Royal Brisbane Hospital, K Floor, Herston, 4006, Australia .
E-mail: davidk@psychiatry.uq.edu.au