

Chapter 10 Comorbidities

This chapter discusses treatment approaches to patients with alcohol-related physical comorbidity, co-occurring mental and alcohol use disorders, and people using multiple drugs (the latter section primarily focusing on people who are polydrug dependent).

Alcohol-related physical comorbidity

Recommendation	Strength of recommendation	Level of evidence
10.1 Comprehensive assessment is indicated for patients with physical comorbidity related to alcohol, as multiple pathology is the rule.	A	1
10.2 Abstinence is recommended for those with physical comorbidity related to alcohol unless mild and reversible pathology is present. In particular, pancreatitis may recur after a single drink.	D	IV
10.3 Comprehensive management requires a single practitioner with a broad range of clinical skills or close coordination between an appropriate team.	S	

People with alcohol use disorders often have associated physical comorbidities. These include peripheral neuropathy, brain damage, liver disease, gastritis and pancreatitis; heart and vascular diseases, nutritional disorders (e.g. malnutrition or thiamine deficiency), metabolic disorders (e.g. hypoglaecemia), endocrine deficiencies (e.g. reduced fertility) and cutaneous problems (e.g. porphyria, psoriasis, excema); malignancies, and infections (see table).

Accidents, injuries and poisonings are also associated with excessive alcohol use and intoxication (Adrian and Barry 2003). Adrian et al compared the nature and extent of treated health problems in patients with problems related to the use of alcohol and drugs (including both licit and illicit drugs) with the morbidity levels of all patients treated in Ontario, Canada, hospitals for 1985-86, using age-sex standardised morbidity ratios. The morbidities of all inpatients with alcohol or drug diagnoses (n = 52,200) were examined retrospectively through the medical records. Excess morbidity for alcohol patients affected more diagnostic categories and body systems, and was at a higher level than for drug patients. Both had particularly high morbidity for mental disorders, infectious and parasitic diseases, and injury and poisoning (Adrian and Barry 2003). Alcohol dependence and misuse is also implicated in the risk of suicide, especially in the elderly (Waern 2003).

Table 10.1: Alcohol use and physical complications

Gastrointestinal	<ul style="list-style-type: none">• Liver disease, including alcohol-related fatty liver, alcoholic hepatitis, alcohol-related cirrhosis and multiple complications of cirrhosis and portal hypertension• Liver cell cancer – hepatocellular carcinoma• Acute and chronic pancreatitis• Parotid enlargement• Gastro-oesophageal reflux• Peptic ulcer, gastritis, duodenitis• Oesophageal rupture from violent vomiting bouts• Small bowel damage leading to malabsorption• Altered bowel habit with diarrhoea predominating
Cardiovascular	<ul style="list-style-type: none">• Hypertension• High output cardiac failure• Cardiomyopathy• Acute rhythm disturbances in alcohol intoxication• Coronary artery disease
Neurological	<ul style="list-style-type: none">• Cortical atrophy• Cerebellar damage (midline structures maximally affected)• Peripheral neuropathy• Autonomic neuropathy• Wernicke’s encephalopathy• Wernicke–Korsakoff syndrome• Central pontine myelinolysis• Marchiafava–Bignami syndrome• Myopathy• Cerebrovascular accidents• Withdrawal delirium and neuronal damage

Musculoskeletal	<ul style="list-style-type: none"> • Rhabdomyolysis • Compartment syndromes • Gout • Osteopaenia • Osteonecrosis
Haematological	<ul style="list-style-type: none"> • Thrombocytopaenia from bone marrow suppression • Pancytopenia from hypersplenism • Haemolytic anaemia with advanced liver disease - spur cell anaemia • Macrocytic anaemia • Folate and B12 deficiency anaemias • Coagulopathies from liver disease
Immunological	<ul style="list-style-type: none"> • Impaired B and T cell function mediated by alcohol toxicity • Autoimmune phenomena triggered by acetaldehyde adducts acting as immunogenic targets • IgA nephropathy
Respiratory	<ul style="list-style-type: none"> • Increased predisposition to respiratory infection • TB as a common infection • Aspiration pneumonia • Sleep apnoea
Endocrine	<ul style="list-style-type: none"> • Syndrome of inappropriate antidiuretic hormone secretion (SIADH) • Altered thyroid function • Altered oestrogen metabolism associated with liver damage • Masculinisation in women • Pseudo Cushing's disease • Altered calcium and bone metabolism • Hypoglycaemia • Aggravation of diabetes mellitus • Ketoacidosis • Hypertriglyceridaemia • Testicular atrophy • Hypoparathyroidism
Renal	<ul style="list-style-type: none"> • IgA nephropathy

Infectious diseases	<ul style="list-style-type: none"> • Hepatitis C virus • Pneumonia • Tuberculosis • Sexually transmitted diseases
Nutritional disorders	<ul style="list-style-type: none"> • Vitamin and mineral deficiencies; B1, B6, riboflavin, niacin, calcium, phosphate, zinc, magnesium. • Protein calorie malnutrition
Alcohol and malignancy	The risk of developing certain malignancies increases from base risk levels with any alcohol consumption. These include breast, oropharyngeal and oesophageal cancers. Other malignancies such as colon, pancreatic, hepatic and ovarian are more prevalent in those drinking more than 40 gm per day.

Whereas low or moderate alcohol consumption can be cardioprotective, heavy drinking is associated with increased risks of hypertension, coronary heart disease, and ischemic stroke, possibly due to alcohol-induced sympathetic activation. Chronic excessive alcohol consumption is a strong risk factor for various types of cancer, particularly of the respiratory tract, but also of the digestive system, liver, breast, and ovaries, while heavy drinking is associated with various forms of alcoholic liver disease such as cirrhosis. Alcohol dependence is also a major cause of mortality and is associated with psychiatric conditions, neurologic impairment, cardiovascular disease, liver disease, and malignant neoplasms. Dependence also increases the risk of injury, possibly due to alcohol-related factors such as diminished coordination and balance, increased reaction time, and impaired attention, perception, and judgement (Cargiulo 2007).

A meta-analysis carried out by Corrao et al on the risk of 14 major alcohol-related neoplasms and non-neoplastic diseases plus injuries showed, from 156 studies with 116,702 patients, strong trends in the risk for cancers of the oral cavity, oesophagus and larynx, hypertension, liver cirrhosis, chronic pancreatitis, and injuries and violence. Weaker direct trends were observed for cancers of the colon, rectum, liver, and breast (Corrao et al. 2004). For all these conditions, significant increased risks were found at ethanol intake of 25g per day. Threshold values were observed for ischemic and hemorrhagic strokes. For coronary heart disease, a J-shaped relation was observed with a minimum relative risk of 0.80 at 20 g/day, a significant protective effect up to 72 g/day, and a significant increased risk at 89 g/day. No clear relation was observed for duodenal ulcer. The authors conclude that there was no clear evidence of a threshold effect for both neoplasms and several non-neoplastic diseases.

A European study investigated physical health problems among patients with alcohol use disorders at alcohol treatment agencies in six European cities (Gossop et al. 2007). The sample comprised 315 patients with a primary alcohol use disorder. Data were collected at admission to treatment using a structured research protocol, and ratings were made by a doctor after a physical examination of the patient. Physical health problems were extremely common: 79% of the sample had at least one, and 59% had two or more problems. These were often serious, and 60% had at least one problem that required treatment. The most common were gastrointestinal and liver disorders, but about a quarter of the sample had cardiovascular or neurological problems. Frequency of drinking, duration of alcohol use disorder, and severity of

alcohol dependence were associated with increased physical morbidity. Current smoking status and age were also associated with poorer physical health. Older drinkers had more physical health problems, although they were less severely alcohol dependent than the younger patients. The authors conclude that the high prevalence of physical health problems among problem drinkers provides opportunities of screening for alcohol use disorders, not only in specialist alcohol treatment services but also in other health-care settings. They recommend that alcohol treatment agencies should provide a full routine health screen of patients at admission to treatment with provision or referral to appropriate treatment.

The most commonly alcohol-associated physical condition is alcohol-related liver disease, either fatty liver or cirrhosis. Alcohol-dependent individuals die from cirrhosis at a much higher rate than does the general population (Cargiulo 2007). However, patients with alcoholic liver disease have been considered less desirable liver transplant candidates than patients with other types of liver disease (DiMartini et al. 2004). These authors examined the pre-transplant prevalence of comorbid physical and psychological problems in 112 alcoholic liver disease patients who received a liver transplant. Fifty-six percent of the patients had comorbid hepatitis C or hepatitis B, 40% had used other substances in addition to alcohol, 25% met the criteria for a lifetime DSM-IV non-alcohol substance use disorder, 36% for a lifetime depressive disorder, and 12% for a lifetime anxiety disorder. They recommend that pre-transplant psychiatric evaluation should be undertaken with alcoholic liver disease patients to identify other substance use disorders and other psychiatric disorders that may require treatment prior to admission.

Vascular diseases are another complication associated with alcohol consumption. Epidemiologic studies have shown a J-shaped association between alcohol consumption and vascular diseases, as also demonstrated in the meta-analysis above (Corrao et al. 2004). However, only a few studies have reported on the association between alcohol intake and subclinical atherosclerosis.

The aim of a German study (Schminke et al. 2005) was to investigate the relation between alcohol intake and carotid intima-media thickness (IMT) in participants in a very large study, the population-based Study of Health in Pomerania. In 1230 men and 1190 women, the mean IMT of the right and left common carotid arteries was measured by ultrasonography. Alcohol consumption was assessed at interview, calculating the quantities of alcohol consumed from the ethanol content of the specific drinks reported by patients. Linear regression controlled for age, diabetes, systolic blood pressure, physical activity, eating patterns and frequency, smoking status, and education revealed a significant inverse association between IMT and alcohol intake ≤ 80 g/d in men ($p < 0.02$), which became insignificant after further controlling for HDL cholesterol and fibrinogen. In women, no significant differences in IMT were found between the two groups. The authors can conclude that alcohol consumption was inversely correlated with carotid IMT in men but not in women; however, the reported total daily level of alcohol intake was above the threshold where severe alcohol related comorbidity and organ damage have been reported, and correspondingly any potential protective effect of alcohol was accordingly lost.

Another study describes the relation between eating disorders and alcohol and drug abuse (Conason et al. 2006). Eating-disordered patients are already at an increased risk for morbidity and mortality, so that alcohol and drug use pose additional dangers for these patients. Anorexics, binge eaters, and bulimics appear to be distinct subgroups within this population, with binge eaters and bulimics more prone to alcohol and drug use. Impulsivity has also been linked to both bulimia nervosa and

substance abuse. The authors say that interviewing is generally the most useful tool in diagnosing alcohol and substance abuse disorders in these individuals (rather than questionnaires etc), and they also recommend obtaining information from third parties as patients may be unwilling to disclose their substance use.

The above studies suggest that all patients with alcohol use disorders should be carefully assessed for physical (and psychological) comorbidities that would otherwise be overlooked in treating the primary presenting condition. Abstinence from alcohol is to be recommended for patients with comorbid physical problems, especially pancreatitis (Strum 1995; Pelli et al. 2008; Tsujimoto et al. 2008) to improve their quality of life and relief from pain.

Co-occurring Mental Disorders

Introduction

In Australia, of the 10,641 people surveyed for the National Survey of Mental Health and Well Being in 1997, 1.9 percent met the criteria for alcohol abuse, and 4.1 percent met the criteria for alcohol dependence. Of this latter group around one in five (20 percent) met criteria for an anxiety disorder and almost one in four (24 percent) met criteria for an affective or mood disorder. Other disorders associated with alcohol dependence include other substance use disorders and psychosis (Degenhardt et al. 2000).

One rural New South Wales health service's data showed that 43% of inpatient and 20% of ambulatory mental health admission records indicated problem drinking or drug-taking. Information gathered from focus groups conducted with consumer groups and service providers indicated a reasonable level of awareness of co-morbidity, and changes were underway to better meet patient needs; however, the results indicated a lack of formalised care coordination, unclear treatment pathways, and a lack of specialist care and resources to treat such patients (Hoolahan et al. 2006).

Indig et al. (2007) looked at presentations to Emergency Departments (ED) in New South Wales and found that high-risk alcohol consumption, high psychological distress and current smoking were all significantly and independently associated with a greater likelihood of presenting to an emergency department in the last year. ED presentation was found to be three times more likely for women aged 30-59 years with all three risk factors, and ten times more likely for women aged 60 years or more who reported high risk alcohol consumption and high psychological distress, than similar-aged women without these risk factors. For individuals aged 16-29 years, being a high-risk drinker and a current smoker doubled the risk of presentation to ED. The authors conclude that the combination of being a high-risk consumer of alcohol, having high psychological distress, and being a current smoker are associated with increased presentations, independent of age and sex.

Scher et al studied 505 depressed subjects with and without co-occurring alcohol use disorders (AUDs) between 2000 and 2005 (Sher et al. 2008). A total of 318 had DSM-IV major depressive disorder without a history of any alcohol or substance abuse/dependence and 187 had depression and a history of alcohol abuse/dependence. Demographic, clinical, and psychiatric history measures of patients in the two groups were examined and compared. Dual diagnosis patients

were significantly younger at their first psychiatric hospitalisation, their first major depressive episode, and their first suicide attempt. They reported more previous major depressive episodes, suicide attempts, and recent life events and had higher lifetime aggression, impulsivity, and hostility. These patients were also more likely to report tobacco smoking, a lifetime history of abuse, and a history of alcohol problems among first-degree relatives, compared to depressive patients. They also had significantly higher childhood, adolescent and adult aggression scores and reported more behavioural problems during childhood. Scher's findings suggest that in addition to obtaining a history of depression and suicidal behaviour, clinicians should also assess for an alcohol use disorder; conversely patients with alcohol use disorders should be assessed for depression. Comorbidity may result from worse antecedents and lead to early onset, more comorbidity, and a more severe course of illness.

Co-occurrence of anxiety and depressive symptoms with alcohol consumption/abuse was analysed by Almeida-Filho et al in a sample of 2,302 adults in Bahia, Brazil (Almeida-Filho et al. 2007). A cross-sectional household survey collected self-reported information on social and personal health, as well as individual psychological status. Prevalence was 15% for anxiety, 12% for depressive disorders and 7% for alcohol abuse/dependence. Symptom co-occurrence was more frequent for depression (94% of cases), followed by anxiety disorders (82%), and alcoholism (20%). There was a 74% prevalence of anxiety symptoms among depressives, and a 61% of anxiety sufferers also suffered depression. The combination of depression plus anxiety was the most prevalent, ranging from 17% for women to 5% for men.

Levander et al (2007) conducted a structured clinical interview for DSM-IV with bipolar men and women. They were then divided into (i) subjects meeting current or lifetime criteria for an alcohol use disorder ($n = 213$), and (ii) those subjects who did not ($n=137$). Lifetime rates of comorbid anxiety disorder were evaluated between groups. Their results showed that of 350 subjects, 163 (46.5%) met criteria for an anxiety disorder. Panic disorder and obsessive compulsive disorder (OCD) were the most common anxiety disorders in both groups. OCD and specific phobia were significantly less prevalent in patients with alcohol use disorders than those without, and bipolar women with an alcohol use disorder had a significantly higher rate of post-traumatic stress disorder than those without.

Thus there is clear evidence for increased prevalence of mental disorders in people with alcohol use disorders. The co-occurrence of mental and alcohol use disorders presents special challenges in the treatment of individuals with alcohol problems. There is some evidence that the co-occurrence is associated with greater disability and poorer response to treatment (Schneider et al. 2001; Farrell et al. 1998; Project MATCH Research Group 1997; Terra et al. 2006; Tomasson and Vaglum 1996; Tomasson and Vaglum 1998a). In addition, a higher readiness to change problem drinking has been found in outpatients with dual diagnoses (Velasquez et al. 1999), although it could also be that the more psychiatric distress the person is experiencing, the more tempted they are to drink.

There are diagnostic dilemmas. Some of the co-occurrence appears to be a direct or withdrawal effect of alcohol which remits with abstinence of at least three weeks duration (Schuckit and Hesselbrock 1994; Schuckit and Monteiro 1988). In other cases mental disorders are in parallel with alcohol use disorders. Still further cases show signs of mental disorders and alcohol interacting to cause greater problem severity, disability and poorer response to treatment.

Recommendation	Strength of recommendation	Level of evidence
10.4 Patients with comorbid disorders of alcohol use and persisting mental health comorbidity should be offered treatment for both disorders.	A	1b
10.5 More intensive interventions are needed for comorbid patients, as this population tends to be more disabled and carries a worse prognosis than those with single pathology.	B	I

Assessment and diagnosis

Firstly, given the high prevalence of other disorders amongst patients with an alcohol use disorder, it is essential that checking for particularly common problems such as anxiety and depression symptoms is a routine part of the assessment. Secondly, the AUDIT appears to be a suitable screening tool for identifying risky, problem and dependent alcohol consumption amongst psychiatric patients (Cassidy et al. 2008; Dawson et al. 2005). Physical comorbidities and sociodemographic factors have an effect on neurocognitive functioning and also need to be assessed (Durazzo et al. 2008).

Recommendation	Strength of recommendation	Level of evidence
10.6 AUDIT is recommended for screening psychiatric populations.	A	Ib

The key issue in the assessment of co-occurring mental disorders is whether they are an effect of alcohol or a separate comorbid disorder. Some epidemiological data suggest that social phobia but not panic disorder begins before alcohol consumption and may have a distinct genetic vulnerability (Merikangas et al. 1998) suggesting that the age of onset may be one way to determine whether co-occurring symptoms of mental disorders are an artefact of alcohol consumption or withdrawal. A period of abstinence is the most widely used method to make a differential diagnosis (Brown et al. 1991; Schuckit et al. 1994; Schuckit et al. 1988).

It may be possible to differentiate between primary and secondary depressive disorders, which may have implications for treatment strategies, since secondary depression often abates once the alcohol use disorder is addressed (Schuckit et al. 1997). In this study, individuals who met DSM-III criteria for alcohol dependence were selected from a particular ongoing US cohort study. Almost 42 percent of dependent drinkers met criteria for a diagnosis of a concomitant major depressive episode. Of those, more than 60 percent reported a substance-induced period of depression. Those with primary depression also had a higher prevalence of independent depressive disorders in first-degree relatives. These individuals typically had experience with fewer drugs and less treatment for alcohol problems and were more likely to have attempted suicide. However, the clinical presentation of

symptoms did not differ substantially between substance-induced and primary depressive disorders.

Recommendation	Strength of recommendation	Level of evidence
10.7 Assessment for comorbid disorders should take place once the patient's withdrawal syndrome has diminished, since some anxiety and depressive symptoms may abate once alcohol consumption is reduced or ceased.	B	II

Co-occurring alcohol dependence and mental disorders: Reviews and meta-analyses

A study in the USA by Sullivan et al (2005) reviewed the literature looking for answers to the following questions. How common are alcohol problems in patients with depression? Does alcohol affect the course of depression, response to antidepressant therapy, risk of suicide/death, social functioning and health care utilisation? In which alcohol categories and treatment settings have patients with depression and alcohol problems been evaluated? Studies were selected using predefined criteria of reporting on either the prevalence or the effects of alcohol problems in depression. Thirty-five studies were included and revealed a median prevalence of current or lifetime alcohol problems in depression of 16% (range 5-67%) and 30% (range 10-60%), respectively, compared to 7% for current and 16-24% for lifetime alcohol problems in the general population. The majority of the studies evaluated alcohol abuse and dependence, and 25 of 35 (71%) were conducted in psychiatric inpatients. They found evidence that antidepressants improved depression outcomes in persons with alcohol dependence. Alcohol problems were associated with worse outcomes with respect to course of depression, suicide/death risk, social functioning, and use of health care services. The authors conclude that alcohol problems are more common in depression than in the general population, are associated with adverse clinical and health care outcomes, and that antidepressants can be effective in treatment of depression associated with alcohol dependence. In addition, one of the drawbacks of their search was that the literature they found seemed to focus almost exclusively on patients with alcohol use disorders, including dependence, in psychiatric inpatient locations, and excluded individuals with less severe alcohol problems and in outpatient settings.

Davis et al (2008) reviewed a recent systematic research on distinguishing baseline characteristics, including demographics and the influence of family history, clinical features such as depressive symptoms and suicidal ideation, and the outcome of treatment for depression, in patients with comorbid major depressive disorder and substance use disorders. They also addressed the possible explanations cited in the literature as to why these two disorders tend to co-occur and the implications of the comorbidity of these illnesses on treatment. Their findings showed that nearly one-third of patients with a major depressive disorder also had a substance use disorder, and the comorbidity resulted in a higher risk of suicide and greater social and personal impairment, as well as other psychiatric conditions. Although the treatment of comorbid major depressive disorder and substance use disorders with medication can often be effective, this has not yet been the subject of many rigorous studies to

date. The authors' conclusions are that the emerging results of recent studies comparing the outcome of major depressive disorder patients with comorbid major depressive disorder and substance use disorders suggest that there are fewer differential effects based on comorbidity than previously anticipated by older assumptions from smaller, less methodologically rigorous studies.

Degenhardt and Hall described patterns of co-morbidity between alcohol use and other substance use problems in the Australian population using data from the 1997 National Survey of Mental Health and Well-Being (Degenhardt, Louisa and Hall 2003). Multiple regression analyses examined whether the observed associations between alcohol and other drug use disorders were explained by other variables, including demographic characteristics and neuroticism. They also assessed whether the presence of co-morbid substance use disorders affected treatment seeking for a mental health problem. Alcohol use was related strongly to the use of other substances; those who did not drink alcohol within the past 12 months were less likely to report using tobacco, cannabis, sedatives, stimulants or opiates. Half (51%) of those who were alcohol-dependent were regular tobacco smokers and one-third had used cannabis (32%); 15% reported other drug use; 15% met criteria for a cannabis use disorder and 7% met criteria for another drug use disorder. Co-morbid substance use disorders (sedatives, stimulants or opioids) predicted a high likelihood of seeking treatment for a mental health problem among alcohol-dependent people.

Anxiety: impact on treatment of alcohol dependence

There are several studies that have addressed the impact of comorbid anxiety disorders on outcomes of treatment for alcohol dependence. Evidence from these is conflicting. Results from some of the earlier studies (Tomasson and Valgum 1996, 1998a, 1998b; Driessen et al. 2001) suggest that comorbidity is associated with worse alcohol treatment outcome, relapse and readmissions.

Tomasson's 1996 study (Tomasson and Valgum 1996) looked at the association between psychopathology and alcohol consumption in a sample of inpatient dependent alcoholics (n = 245) who were examined at intake and at 15 month follow-up. At baseline, men and women with antisocial personality disorder or cognitive impairment consumed more alcohol in the month prior to admission than those without these disorders. In contrast, men with panic disorder drank less than those not so affected. The prognosis for men consuming more than the median amount of alcohol was worse than that of women. However, after controlling for psychiatric distress and alcohol consumption at baseline, the prognosis of women was worse. Women who had stopped drinking had a higher degree of psychiatric distress at follow-up compared with those still drinking at a low level. Among men, panic disorder predicted continued drinking. Psychiatric distress and alcohol consumption at baseline both interacted to predict alcohol consumption at follow-up.

Another study by the same authors (Tomasson and Valgum 1998a) was a prospective study over a 28-month period in Iceland using a representative sample (n = 351), examining the association among patients seeking detoxification between comorbid psychopathology and (1) number of lifetime admissions, (2) readmissions for detoxification, and (3) a repeating (revolving-door) pattern of admission (>4 admissions within 30 months). Patients with no comorbid diagnoses had the fewest lifetime admissions. Agoraphobia or panic disorder predicted readmission (odds ratio 5.8) for those with fewer than two prior admissions. For those with 3 or more prior admissions, readmissions were primarily related to polysubstance abuse. The development of the revolving-door pattern was rare (6%) among those with less than

4 prior admissions. Among others (27%), it was primarily predicted by polysubstance abuse.

Another Tomasson study (Tomasson and Valgum 1998b) produced similar results in that polysubstance use had clear implications for worse outcomes. Controlling for alcohol consumption, polysubstance abuse predicted accidents (odds ratio, OR = 2.9) and fights (OR = 3.9) among men, while phobia (OR = 4.3) and antisocial personality disorder (OR = 3.0) predicted fights in both men and women.

A cluster analysis by Driessen et al (2001) examined the association between drinking behaviour and the course of anxiety and depression in 100 alcohol dependent patients with and without these comorbid disorders during the early and late post-detoxification periods. At 6 months, abstinence rates differed significantly between groups: 60.5% non-comorbid vs. 30.5% comorbid anxiety and depression vs. 23.5% anxiety alone). Although not definitive, it appears that comorbid anxiety disorders may be associated with a poorer treatment outcome for alcohol dependence.

However, in contrast, Marquerie et al (2006) examined whether the outcome of treatment-seeking alcohol dependent patients with a comorbid phobic disorder was worse than that of similar patients without comorbidity. The probabilities of resuming drinking and relapsing into regular heavy drinking in 81 alcohol-dependent patients with comorbid social phobia or agoraphobia were compared with 88 alcohol-dependent patients without anxiety disorders. Their results showed that the risk ratio for the association of phobic disorders with resumption of drinking was 1.05, ($p = 0.66$) and the adjusted hazard ratio for the association of phobic disorders with a relapse into regular heavy drinking was 1.02 ($p = 0.89$). The findings of this study did not confirm the idea that alcohol-dependent patients who have undergone treatment are at greater risk of a relapse if they have a comorbid anxiety disorder. No differences were found in abstinence duration or time to relapse into regular heavy drinking between patients with and without comorbid phobic disorders.

In addition, Terra et al (2006) in Brazil investigated the impact of social phobia on adherence to and outcomes 6 months following standard alcohol treatment and Alcoholics Anonymous group meetings among alcohol-dependent patients with and without social phobia. Alcohol-dependent patients ($n = 300$) were interviewed during admission for detoxification and at 3 and 6 months afterwards. At both follow-ups, treatment adherence was low and relapse rates were high among both groups of patients, and no significant differences were seen between the two groups in amount of relapse, adherence to AA, or adherence to psychotherapy. Although the social phobics showed a tendency to be less committed to treatment, or felt less integrated with their AA group, social phobia was not a significant risk factor for alcohol use relapse or loss of adherence to psychotherapy.

Treatment

Co-occurring mental and substance use disorders should be managed in parallel with evidence-based treatments provided for both problems (Horsefall et al. 2009).

Comorbid mental disorders that do not abate within 3 to 6 weeks of abstinence (or significantly reduced drinking) or that emerge from such a period should be treated

according to the clinical practice guidelines for those specific disorders (Tiet and Mausbach 2007).

Limited evidence supports integrating the content of treatment (Tiet and Mausbach 2007; Hesse 2009). Patient engagement in treatment planning and goal setting is particularly important in this population of patients. Adequate duration of treatment is essential to successful outcome. Clinicians should emphasise the patient's education and rising awareness of the interaction between alcohol use and symptoms of mental disorder. Patients with comorbid mood and alcohol use disorder should be regularly assessed and monitored for risk of suicide.

Brief interventions

Grothues et al (2008b) examined the effectiveness of brief interventions in general practice patients with comorbid anxiety or depressive disorders, because of the recent strong evidence that brief interventions are effective in this setting (Kaner et al. 2007). In an RCT with two intervention groups and one control group, data were collected from 408 patients with alcohol use disorders, at-risk drinking or binge drinking; 88 patients were diagnosed with comorbid anxiety and/or depression. The effectiveness of brief intervention (BI) was assessed at a 12-month follow-up in relation to the presence and absence of comorbidity. Reduction of drinking in six ordered categories (g/alcohol) between baseline and follow-up served as the outcome variable. The brief intervention was significantly effective in reducing drinking in the non-comorbid ($p = 0.03$) but not in the comorbid patients ($p = 0.76$). As brief interventions are known to be less effective for dependent drinkers, a larger proportion of dependent drinkers in this group might have limited their effectiveness.

Grothues et al also tested the theory that the comorbid patients would seek help more often than the others after brief intervention (Grothues et al. 2008a), using data from patients participating in the above study. At 12-months follow-up, differences in help-seeking for drinking problems were assessed between comorbid and non-comorbid individuals. In a logistic regression analysis, comorbidity ($p = 0.01$) and previous help seeking ($p < 0.001$) were found to be positive predictors for utilising formal help. The authors conclude that individuals with problematic drinking and comorbid anxiety or depressive disorders might benefit from more specialised support.

Psychosocial interventions

Comorbid mental disorders that last beyond a 3 to 6 week period of abstinence (or significantly reduced drinking) or that emerge from such a period should be treated according to the clinical practice guidelines for those specific disorders. The service that provides care should be integrated, but little evidence supports use of specific packages that integrate the content of psychological interventions. The psychosocial treatments discussed in Chapter 6 can be tailored to individual needs. Regardless of whether services follow integrated or parallel models, they should be well coordinated and provide for long-term follow-up (Tiet and Mausbach 2007; Harsefall et al. 2009; Hesse 2009).

Depression

In one study, cognitive behavioural therapy (CBT) was shown to have greater benefits for depressed alcohol dependent patients than standard alcohol treatment combined with relaxation training (Brown et al. 1997). Thirty five participants with a diagnosis of DSM-III-R alcohol dependence and a Beck Depression Inventory score

of 10 or greater were recruited from an alcohol and drug treatment service day hospital program at a psychiatric hospital. Women made up 29 percent of the participants in the study. Participants received either CBT or relaxation training with the standard day hospital treatment. Post-treatment, patients in the CBT group had greater reductions in depressive symptoms and a higher percentage of days abstinent than the standard treatment group. At three and six-month follow-up, the CBT group also had significantly better outcomes for total abstinence (47 percent vs. 13 percent), proportion of days abstinent (91 percent vs. 68 percent), and drinks per day (0.46 vs. 5.71).

Kavanagh et al (2006) reported that cue exposure and cue exposure with a negative mood induction did not significantly add to CBT, based on the work of Sitharthan in reducing drinking or depression (Sitharthan et al. 1996). The patients in this RCT drank when they were dysphoric, but those with current major depressive episodes were excluded.

Anxiety

The effect of anxiety management procedures such as relaxation training in more severely dependent drinkers has shown reductions in anxiety but not in drinking. Ormrod and Budd (1991) compared a multi-component cognitive behavioural anxiety management program and a progressive muscle relaxation program with a health education control group for outpatients with anxiety and alcohol problems. Both anxiety management and relaxation training reduced anxiety levels compared with the control group but there was no difference in drinking outcomes. Those who reported that they drank to reduce anxiety were no more likely to show reductions in drinking from an anxiety-reducing intervention than those who reported no such link. The study analysis was, however, limited by its small sample size (n=36).

Lehman, Brown and Barlow (1998) report on three cases of people suffering panic disorder and agoraphobia and co-existing alcohol abuse who were treated with CBT for panic disorder and agoraphobia which ignored their alcohol use. At a six month follow-up only one had a diagnosis of alcohol abuse. These patients did not meet criteria for alcohol dependence, and, from their histories, it appears that the two whose alcohol use had declined from diagnostic levels had milder initial drinking patterns. These patients sought help from a specialist anxiety disorders clinic and were motivated to deal with their panic disorder and agoraphobia.

Bowen et al. (2000) found that for alcohol dependent patients with comorbid panic disorder, CBT was no better than a standard alcohol treatment program in reducing problem drinking. Participants were randomised to receive either CBT (n = 146) or the standard alcohol treatment (n = 85). Follow-ups were conducted at three, six and twelve months. The CBT treatment consisted of six-two hour group-based panic management training sessions. The article does not describe the standard treatment program, but the authors suggest that it may have contained enough active anxiety-treatment ingredients to reduce any differences between it and CBT.

One sub-analysis of data reported that CBT delayed relapse for female, alcohol dependent patients with comorbid social phobia. Using data from Project MATCH, patients receiving CBT were compared with those who received 12-step facilitation. Socially phobic women, but not men, who received CBT had a longer time to relapse than matched counterparts in the 12-step group, and for socially phobic males, there was a trend towards better outcomes in the 12-step group (Thevos et al. 2000).

In contrast, Bowen, D'Arcy Keegan and Senthilselvan found that for alcohol dependent patients with comorbid panic disorder, CBT was no better than a standard alcohol treatment program in reducing problem drinking (Bowen et al. 2000). Participants were randomised to receive either CBT (n = 146) or the standard alcohol treatment (n = 85). Follow-ups were conducted at three, six and twelve months. The CBT treatment consisted of six-two hour group-based panic management training sessions. Unfortunately the article does not describe the standard treatment program, but the authors suggest that it may have contained enough active anxiety-treatment components to reduce any differences between it and CBT. While the sample size was initially large, nearly a third (46) dropped out of the CBT group; however there was still sufficient power to compare groups. There were no statistically significant differences between the groups on anxiety or drinking outcomes. One of the possible explanations given by the authors is the resistance from other staff to introducing the program, and the relatively brief nature of the CBT intervention. They also raise the possibility that the anxiety disorder experienced by people with co-existing substance use disorders may be different from those who have no co-existing problems.

One study found that treatment for both alcohol dependence and social phobia produced worse alcohol use outcomes than treatment for alcohol dependence alone (Randall et al. 2001). A total of 93 participants were randomised to either 12 weeks of CBT for alcoholism only or concurrent treatment for both alcohol and social anxiety problems. Participants were followed up after the 12 weeks and again three months after the end of treatment. Whilst both groups improved on alcohol-related and social anxiety outcomes, the dual treatment group had worse outcomes than the alcohol dependence treatment group on three of the four alcohol use measures. They also reported no significant correlation between reductions in drinking and social anxiety measures indicating the processes of change for these two outcomes were unrelated. A lack of integration between the CBT for social phobia and alcohol and resulting patient confusion may account for the lack of additional effects for additional anxiety treatment.

The unexpected finding of worse alcohol outcome in the dual treatment group in the above study (Randall et al. 2001) was attributed to several limitations, including individual rather than group treatment when group anxiety treatment is regarded by some as the preferred mode; parallel presentation of two unintegrated manualised treatments, in which alcohol was addressed during the first 45 minutes of each session and social phobia in the next 45 minutes; and a loss of alcohol treatment time in the dual treatment condition. The authors comment that the sample was drawn from "severe population of treatment-seeking alcoholics". Thus those with higher initial alcohol dependence may not do as well if they are distracted from a focus on their alcohol problems. In addition, the intervention for social phobia was based on an unknown treatment manual (Holmstrom and Thevos, 1993, unpublished) the efficacy of which cannot be determined. An intervention supported by empirical evidence may have yielded different results.

Another study of alcohol dependence and social phobia (Schadé et al. 2005) was a randomised controlled trial of 96 abstinent alcohol dependent patients with comorbid anxiety disorder (social phobia or agoraphobia). The patients were randomly assigned to an intensive, comprehensive 32 week psychosocial program, involving 3-4 months of inpatient groups followed by up to 16 weeks of aftercare, relapse-prevention and disulfiram on its own or in combination with an anxiety treatment program comprising CBT and optional pharmacotherapy. The anxiety treatment consisted of 12 weekly 60-minute sessions of cognitive therapy delivered individually

at an anxiety clinic; the first six sessions of treatment dealt with alcohol only. The authors found that additional therapy for anxiety significantly reduced anxiety symptoms and avoidance behaviour but did not affect the alcohol relapse rates. While 13 of the 49 (26%) who were allocated to Alcohol only treatment were abstinent for 30 days before each of the three assessments, 18 of the 47 (38%) who were allocated to alcohol and anxiety treatment were similarly abstinent, giving an effect size of 0.13. While this difference was not statistically significant there was only a 23% chance that this size of effect would be detected with this sample size. In addition there was a trend of greater reduction of heavy drinking days in the dual treatment group: the reduction in mean number of days drinking 5 or more drinks from baseline to follow-up, was greater (but not significantly) in the combined (mean reduction 9.4) than in the alcohol-only treatment (mean 7.1). The inclusion of both panic/agoraphobia and social phobia comorbidities with alcohol use disorder leaves the results less clear.

Schade et al (2007) report on predictors of outcome in the 34 completers in their combined phobia and alcohol treatment groups. While severity of alcohol dependence did not predict anxiety outcomes, later age of onset for alcohol problems was related to better anxiety outcomes.

One quasi-randomised experiment was carried out by Nielsen et al (2007). They theorised that personality-guided treatment for alcohol dependence, an approach that integrates cognitive therapy for addictive behaviours with a strategic intervention for certain personality traits, may be helpful for patients with co-morbid alcohol dependence and personality disorders. They compared patients admitted for alcohol dependence in Denmark (n = 108) and allocated them to either standard inpatient treatment with cognitive therapy for alcohol dependence, or to the personality-guided treatment. Follow-up was conducted by mail at six months after treatment. Personality-guided treatment was associated with better retention, longer time to first relapse, and less time spent drinking post-treatment, although few differences reached statistical significance. Differences in results were mainly found in the subgroup with higher levels of personality disorder. These results suggest that personality-guided treatment is a promising approach, directed at the particular personality disorders and the typical function fulfilled by drinking. This complex instrument is described in the article, but it is available only in Danish.

Psychosis and chronic mental disorders

A recent update by Cleary et al (2008) was conducted of Ley et al's (2000) Cochrane Review of Psychosocial Interventions for people with both severe mental illness and substance misuse. They suggest that the evidence is poor at best, with very few studies. They examined 25 RCTs and found no compelling evidence to support one psychosocial treatment over another to reduce substance use or improve mental state for people with a serious mental health problem.

We just mention a few positive studies here. Integrating motivational interviewing, CBT and family intervention with routine psychiatric care produced greater benefits for patients with comorbid schizophrenia and substance use disorders than routine psychiatric care alone (Barrowclough et al. 2001). Thirty-six participants and their caregivers were randomised to receive either (i) motivational interviewing, CBT and family intervention plus routine care or (ii) routine care alone. At 12-month follow-up, the integrated treatment group had better general functioning, a reduction in positive symptoms, and an increase in the percentage of days abstinent from alcohol or drugs.

Herman et al (2000) randomly assigned patients with a serious mental illness and a substance use disorder to either an integrated mental health and substance use treatment program or to a standard hospital treatment program. A total of 429 participants were randomised at a ratio of 2:1 into either the integrated treatment or the standard short-term treatment ward. Two months after treatment, those receiving integrated treatment had fewer days of alcohol use than those in the standard treatment program. This study also found that patients who had no family involvement, low intentions to stay sober and who had low attendance at self-help groups post-treatment had the worst outcomes.

In a more recent study Salloum et (2005) reported on a 24-week double-blind placebo-controlled RCT of divalproex sodium (valproate) for alcohol dependence and bipolar I disorder. In 59 patients, valproate led to significant reductions in alcohol but had no differential effect on bipolar outcomes compared to placebo.

Graeber et al (2003) conducted a pilot study with 30 patients who had comorbid schizophrenia and alcohol use disorders. They were randomly assigned to receive either a Motivational Interviewing (MI) or Educational Treatment (ET) intervention with treatment goals of abstinence and/or decreased alcohol use. Subjects were followed up at 4, 8 and 24-weeks after completing the interventions. Outcome measures included number of drinking days, abstinence rates, average blood alcohol concentration and standard ethanol content per drinking day. MI subjects had a significant reduction in drinking days and an increase in abstinence rates when compared to subjects receiving ET. These authors conclude that motivational Interviewing may be a useful adjunct to intervention for individuals with comorbid schizophrenia and alcoholism.

Recommendation	Strength of recommendation	Level of evidence
10.8 Comorbid mood and anxiety disorders that do not abate within 3 to 6 weeks after alcohol withdrawal is complete should be treated with integrated/concurrent cognitive behavioural therapy for the comorbid disorder.	B	II
10.9 Cognitive behavioural therapy, behaviour therapy, cognitive therapy, and interpersonal therapy should be considered for treatment of patients with comorbid mental and alcohol use disorders because of their demonstrated effectiveness in non-comorbid cases.	B	Ib
10.10 Integrating psychosocial treatment for mood disorders and psychoses with psychosocial treatment for alcohol-use disorder may be beneficial in treating patients with such comorbidity.	D	IV

Pharmacotherapy

Pharmacological treatments have proved effective in treating anxiety, depression and psychosis in patients exhibiting co-occurring mental and alcohol use disorders. However they should not be used as primary treatments of alcohol dependence as

there is little evidence that treatment of co-morbid mental disorder alone leads to a reduction of alcohol intake.

Depression

A meta-analysis of randomised controlled trials by Nunes and Levin (2004) indicates that antidepressant medication has a modest beneficial effect for patients with combined depressive and substance-use disorders. It is not recommended as a stand-alone treatment. Concurrent treatment directly targeting substance dependence is also indicated. The findings also suggest a clinical approach that begins with an evidence-based psychosocial intervention, followed by antidepressant medication if depression does not improve.

Evidence for the capacity of SSRIs to reduce alcohol intake is mixed, and several trials have examined the effectiveness of SSRIs with comorbid patients. Three very early studies (Naranjo et al. 1995; Kabel and Petty 1996) found little advantage for SSRIs over placebo in reducing alcohol consumption in the long term (after 12 weeks); however fluoxetine was found to be effective in reducing depression symptoms (Kranzler et al. 1995).

Cornelius et al. (1997) administered fluoxetine or placebo over a 12-week period to a randomised group of 51 alcohol dependent patients diagnosed with major depressive disorder in an inpatient setting. Depression and alcohol consumption ratings were collected weekly during the 12-week period. Both depressive symptoms and total alcohol consumption over the trial were significantly lower in the fluoxetine group than in the placebo group. One 12 week double-blind RCT of patients with post-traumatic stress disorder (PTSD) (Labbate, Sonne et al. 2004) investigated the role of sertraline in the treatment of patients with comorbid PTSD and an alcohol use disorder. Patients (n = 93) were stratified into four groups depending on presence or absence of additional anxiety or depressive disorders and evaluated for the effects of comorbidity on PTSD symptoms, depressive symptoms, and drinking behaviours, hypothesising that additional comorbidity would be associated with poorer outcomes. Patients in all four subgroups showed marked and clinically significant improvement in alcohol drinking behaviours over the course of the study ($p < 0.001$). There were, however, no significant differences among groups. All patients showed moderate improvement in Hamilton Depression Rating Scale scores and a clinician-administered PTSD scale scores. Hence, having additional anxiety or mood disorder comorbidity did not decrease their response to treatment.

Gual et al. (2003) performed a double-blind, placebo-controlled randomised trial of sertraline in recently detoxified alcohol-dependent patients with current depressive symptoms. The objectives of the study were to evaluate the efficacy of sertraline at achieving stable abstinence, at ameliorating depressive symptoms and at improving quality of life in these patients. 83 patients received either sertraline (50-150 mg/day) or placebo for 24 weeks. The primary outcome criteria were the rate of relapse into alcohol consumption and the rate of response on the Montgomery and Asberg Depression Rating Scale (MADRS). At the end of treatment, relapse rates were 23.1% in the placebo group and 31.8% in the sertraline group. Responder rates for depression were 38.5% for the placebo group and 44.2% for the sertraline group. There was no significant difference between treatment groups with either variable. However, when patients were stratified into severe (MADRS score ≥ 26) and moderate (MADRS score < 26) depression at inclusion, a significant treatment benefit with sertraline was observed in the former group. Quality of life, determined by the SF-36, improved in both groups, with more benefit observed for the sertraline group

on mental health items. Sertraline was well tolerated, and the incidence of adverse events was similar in the two treatment groups. The authors conclude that the explanation for the overall good outcome in both treatment groups and for the inability to demonstrate a clear treatment effect may rest in the clinical features of the patients.

In Kranzler's 2006 study, following a 1-week, single-blind, placebo lead-in period, 328 patients with co-occurring major depressive disorder and alcohol dependence were randomly assigned to receive 10 weeks of treatment with sertraline (at a maximum dose of 200 mg/d) or matching placebo (Kranzler et al. 2006). Randomisation was stratified, based on whether initially elevated scores on the 17-item Hamilton Depression Rating Scale (HDRS) declined with cessation of heavy drinking, resulting in a sample of 189 patients with HDRS scores >17 (group A) and 139 patients with HDRS scores < 16 (group B). Results showed that both the depressive symptoms and alcohol consumption decreased substantially over time in both groups. There were no reliable group differences on depressive symptoms or drinking behavior in either group A or B patients. Therefore this study did not provide consistent support for the use of sertraline to treat co-occurring major depressive disorder and alcohol dependence.

Yet another study, of 42 subjects with social anxiety and a co-occurring alcohol use disorder, participated in a 16-week, double-blind, placebo-controlled clinical trial to determine the efficacy of paroxetine for social anxiety in patients with co-occurring alcohol problems (Book et al. 2008). Paroxetine proved to be superior to placebo in reducing social anxiety, as measured by the Liebowitz Social Anxiety Scale total and subscale scores and additional measures of social anxiety.

However, SSRIS still do not appear to have any significant effects on the reduction of alcohol consumption, either during or subsequent to the trial periods of the studies.

Most importantly, Nunes and Levin's 2004 systematic review and meta-analysis which included 14 double-blinded RCTs and 848 patients to quantify the efficacy of antidepressant medications for treatment of combined depression and substance use disorders (Nunes and Levin 2004) reached the conclusion that antidepressant medication exerts a modest beneficial effect for patients with combined depressive- and substance-use disorders. Their principal measure of effect size was the standardised difference between means on the Hamilton Depression Scale (HDS); the pooled effect size from the random-effects model was 0.38 (95% confidence interval, 0.18-0.58). Heterogeneity of effect on the depression scale across studies was significant ($p < 0.02$), and studies with low placebo response showed larger effects. It is clear from their results that when the medication is effective in treating depression, it helps diminish quantity of substance use; however, sustained abstinence or remission is harder to achieve. They conclude that antidepressant medication is not a stand-alone treatment, and concurrent therapy directly targeting the addiction is also indicated.

Torrens et al reviewed the literature for randomised controlled trials on the efficacy of antidepressant drugs in subjects with drug abuse disorders, including alcohol, cocaine, nicotine and opioids, with and without comorbid depression (Torrens et al. 2005). They conducted a meta-analysis of studies that used common evaluation procedures in alcohol, cocaine and opioid dependence. Based on this review, the authors propose some recommendations: (i) the prescription of antidepressants for drug abuse seems only clear for nicotine dependence with or without previous comorbid depression (bupropion and nortriptyline); (ii) in alcohol dependence without

comorbid depression the use of any antidepressant seems not justified and the use of antidepressants in alcohol, cocaine or opioid dependence with comorbid depression needs more studies in well-defined samples, adequate doses and duration of treatment to be really conclusive. They also conclude that SSRIs do not seem to offer significant advantages compared with tricyclic drugs in substance abuse disorders.

Some noradrenergic antidepressants show promise for reducing relapse or drinking in comorbid patients. For example, nortriptyline (a noradrenergic antidepressant) reduces drinking in patients diagnosed with antisocial personality disorder, but not in those patients with affective/anxiety disorders or those without a comorbid disorder (Powel et al 1995).

A controlled trial with desipramine (a tricyclic antidepressant) showed reduced relapse in alcohol dependent patients diagnosed with major depression, but not in those without major depression (Mason et al. 1996). Tricyclic antidepressants should be used with caution in this population due to high risk of poor treatment adherence, abuse and overdose.

There are two fairly recent trials of nefazodone. Hernandez-Avila and colleagues (2004) reported a reduction in alcohol use, but no reduction on depression symptoms (Hernandez-Avila et al. 2004). In contrast, Roy-Byrne et al. (2000) reported no effect on depression symptoms, substance use, or craving for alcohol.

Ondansetron reduced depression in 161 early onset alcohol dependent patients but not in those 160 with late onset (Anton et al. 2006). The effect on drinking was not reported but there was no relationship between antidepressant effects in early onset drinkers and reductions in drinking. Those whose anxiety reduced during treatment also drank less (Sloan et al. 2003).

In addition, Petrakis et al (2006) studied the effects of naltrexone and disulfiram on alcohol dependent veterans with current DSM-IV major depressive disorders, to find that their response was similar to those without current depression; subjects with PTSD had better alcohol outcomes with active medication (naltrexone, disulfiram or the combination) than they did on placebo, while overall psychiatric symptoms of PTSD improved. The results suggest that disulfiram and naltrexone are effective and safe for individuals with PTSD and comorbid alcohol dependence.

In conclusion, antidepressants should not be the first line of treatment in patients with comorbid alcohol use disorders, unless there is high level of suicidal ideation, severe depressive symptoms or a history of pre-existing depressive illness.

Recommendation	Strength of recommendation	Level of evidence
10.11 Selective serotonin reuptake inhibitor antidepressants are not recommended as primary therapy to reduce alcohol consumption in patients with comorbid mood or anxiety disorders.	B	II

Anxiety

Typical pharmacological treatments for anxiety and mood disorders also reduce anxiety and depression when they co-occur with alcohol use disorders. However, treating only a comorbid mental disorder usually does not lead to a reduction of alcohol consumption.

Selective serotonin reuptake inhibitors (SSRIs) reduce symptoms of anxiety in patients with comorbid anxiety and alcohol dependence. They are indicated for treatment of obsessive-compulsive disorder and panic attacks in these patients. However, little sound evidence supports their capacity to reduce alcohol intake in the longer-term in patients with comorbid anxiety disorders.

Buspirone, an anxiolytic, has been tested with anxious alcohol dependent outpatients with some success. Approximately half of the participants met current diagnostic criteria for an anxiety disorder; others had high levels of anxiety. Participants received either buspirone or placebo over a 12-week period, and weekly, manualised, individual CBT which focused on relapse prevention and skills training. Outcomes were measured at the end of treatment and at a six-month follow-up evaluation. Buspirone patients were more likely to remain in treatment for the 12 weeks, had reduced anxiety, a slower return to heavy alcohol consumption, and fewer drinking days during the follow-up period (Kranzler et al. 1994).

Benzodiazepines are not recommended for treatment of comorbid anxiety in patients with alcohol-use disorders due to high risk of dependence and a potential synergistic interaction with alcohol.

Recommendation	Strength of recommendation	Level of evidence
10.12 Benzodiazepines are not recommended for treatment of comorbid anxiety in patients with alcohol-use disorders due to high risk of dependence and a potential synergistic interaction with alcohol.	S	

Psychosis

A qualified mental health practitioner usually provides pharmacological treatment of psychotic illness. Atypical antipsychotics appear to be the first line of treatment of comorbid psychotic illness and substance use disorders (Wobrock and Soyka 2009).

Limited evidence shows that among schizophrenic patients, two atypical antipsychotics (risperidone and clozapine) may reduce alcohol misuse, smoking, and possibly some other substance misuse (Kavanah et al. 2002).

Addition of psychosocial support to pharmacological treatment has been shown to be effective in treatment of patients with comorbid psychosis and alcohol use disorders (Drake 2007).

Pharmacotherapy combined with psychosocial interventions

In an early study, Kranzler et al (1995) tested the hypothesis that fluoxetine, when used in combination with relapse prevention psychotherapy, would reduce relapse frequency and severity for alcohol dependent patients. This was a randomised, placebo-controlled trial of fluoxetine (up to a maximum of 60 mg/day) for 12 weeks in combination with weekly psychotherapy for 101 alcohol-dependent subjects. Outcomes were measured at the end of treatment and 6 months later. Placebo-treated subjects were more compliant with the medication regimen and remained in the study longer than fluoxetine-treated subjects. There was significantly less alcohol consumption in both groups during treatment than before treatment, and these effects persisted at follow-up. Although fluoxetine had no significant effects on alcohol consumption, it reduced Hamilton Depression Rating Scale scores more than placebo among subjects with current major depression. The authors concluded that Fluoxetine at a dose of 60 mg/day was not useful for relapse prevention in lower-level alcoholics without comorbid depression. In alcoholics with major depression, the drug may reduce depressive symptoms.

There have been three placebo-controlled trials of sertraline in combination with psychological therapies (Deas et al. 2000; Moak et al. 2003; Oslin 2005). Deas et al undertook a 12-week double-blind, placebo-controlled trial of sertraline plus cognitive behaviour group therapy (CBT) to preliminarily evaluate the efficacy, safety and tolerability of the serotonin reuptake inhibitor, sertraline, in the treatment of adolescents with a primary depressive disorder and a comorbid alcohol use disorder. Subjects were 10 outpatient treatment-seeking adolescents. Baseline assessment included several psychiatric diagnostic instruments (K-SADS, HAM-D, SCID), and the Time-Line Follow-Back method of assessing alcohol consumption. The HAM-D and the Time-Line Follow-Back were performed weekly thereafter. Both groups showed a significant reduction in depression scores with an average reduction between baseline and endpoint HAM-D score of -9.8 ($p \leq 0.001$), although there were no significant group differences. There was an overall reduction in percentage of days drinking ($p < 0.02$) and in drinks per drinking day ($p < 0.002$); however, again there were no group differences. Depression patients who responded tended to have higher baseline percentage of drinking days than non-responders ($p = 0.08$) and the change in HAM-D scores tended to correlate with change in the percentage of drinking days ($p = 0.09$). These data support the evidence that sertraline is safe and well tolerated in the treatment of adolescents with depression and alcohol dependence. Small sample size and the CBT group therapy, which was given to all subjects, may have limited the group differences.

Moak et al (2003) looked at the role of sertraline and CBT for depressed alcohol dependent patients, because while SSRIs have proved effective in the treatment of depression and decreased drinking in some studies, the reported effect of these

medications on alcohol intake had not been consistent. Also, at this time most previous studies had not investigated the use of an SSRI in the context of cognitive behavioural therapy, a known efficacious treatment for both alcoholism and depression. They conducted a randomised placebo-controlled 12-week trial of sertraline combined with individual CBT focussing on both alcoholism relapse prevention and depressive symptoms. There were 82 subjects with either primary major depression (70 subjects) or substance-induced mood disorder and at least 1 first-degree relative with an affective disorder (12 subjects). Depression and alcohol consumption outcomes were measured weekly over 12 weeks. Sertraline was well tolerated and all subjects had decreases in both depression and alcohol use during the study compared with baseline. Subjects who received sertraline had fewer drinks per drinking day than subjects who received placebo, but other drinking outcomes were not different between the 2 treatment groups. Treatment with sertraline was associated with less depression at the end of treatment in female subjects compared with females who received placebo. Lower alcohol consumption during the study was also associated with improvements in depression. The findings in this study suggest that sertraline, compared with placebo, may provide some modest benefit in terms of drinking and also may lead to improved depression in female alcohol-dependent subjects. Additionally, alcohol relapse prevention CBT, delivered with modifications that provide specific attention to depression, appeared to be of benefit to subjects, although this is limited by the study design.

Oslin (2005) tested the efficacy of naltrexone combined with sertraline for the treatment of older adults with major depression and alcohol dependence. The sample was 74 subjects, age 55 and older, who met criteria for a depressive disorder along with alcohol dependence. All subjects were randomly assigned to 12 weeks of naltrexone 50 mg/day or placebo. All subjects also received sertraline 100 mg/day and individual weekly psychosocial support. Treatment response for alcohol consumption and depression was measured during the 12 weeks of treatment. At baseline, subjects were drinking an average of 10.7 drinks per drinking day. The overall results are encouraging; 42% of the subjects had a remission of their depression and had no drinking relapses during the trial. There was no evidence for an added benefit of naltrexone in combination with sertraline, but there was significant correlation between any alcohol relapse during the trial and poor response to depression treatment.

The same group (Oslin et al. 2008) also undertook a 24-week double-blind placebo-controlled study of naltrexone to examine the impact of 3 types of psychosocial treatment combined with either naltrexone or placebo treatment on alcohol dependency over 24 weeks of treatment: (i) Cognitive-Behavioural Therapy (CBT) + medication clinic; (ii) BRENDA (an intervention promoting pharmacotherapy) + medication clinic; and (iii) a medication clinic model with limited therapeutic content. Two hundred and forty alcohol-dependent subjects were also randomly assigned to 1 of 3 psychosocial interventions. All patients were assessed for alcohol use, medication adherence, and adverse events at regularly scheduled research visits. There was a modest treatment effect for the psychosocial condition favouring those subjects randomised to CBT. Intent-to-treat analyses suggested that there was no overall efficacy of naltrexone and no medication by psychosocial intervention interaction. There was a relatively low level of medication adherence (50% adhered) across conditions, and this was associated with poor outcome. Results from this 24-week treatment study demonstrate the importance of the psychosocial component in the treatment of alcohol dependence. Moreover, results demonstrate a substantial association between medication adherence and treatment outcomes.

Summary

The evidence supports the assumption that antidepressants help to relieve depressive symptoms but have little effect on reducing alcohol consumption, unless accompanied and supported by psychosocial treatment. Naltrexone and disulfiram may be safely used to help reduce alcohol consumption in patients with comorbid psychiatric disorders. Psychosocial interventions are recommended for comorbid patients, with or without the addition of pharmacotherapy.

Polydrug use and dependence

Recommendation	Strength of recommendation	Level of evidence
10.13 All patients with alcohol-use disorders should be screened for other substance use using quantity–frequency estimates, or through structured screening instruments such as the ASSIST questionnaire.	D	IV
10.14 Polydrug dependence is typically associated with higher levels of physical, psychiatric and psychosocial comorbidity that should be addressed in comprehensive treatment plans.	D	IV
10.15 Use of other drugs can be affected by cessation or reduction in alcohol use, and treatment plans should address use of alcohol and other drugs together.	D	IV
10.16 Patients undergoing polydrug withdrawal need close monitoring, increased psychosocial care, and increased medication. Consider specialist advice.	D	IV
10.17 Fixed diazepam dosing regimens are preferred for managing alcohol withdrawal in the context of other drug withdrawal, with regular review of dosing regimens. Withdrawal scales (such as CIWA-Ar) need careful interpretation in patients withdrawing from multiple drugs, and should not be used to direct medication.	D	IV
10.18 Patients dependent on alcohol and benzodiazepines or opioids should be stabilised on substitution medications while undergoing alcohol withdrawal.	D	IV

Introduction

There is published evidence from several countries that other substances; legal, illicit or prescribed, are commonly used in combination with alcohol (Martin et al. 1996; Barrett et al. 2006; Brecht et al. 2008; McCabe et al. 2006), but little has been published about the influence of polydrug use on alcohol withdrawal (Degenhardt and Dunn 2008). The last 40 years has seen a rapid expansion in the availability, range and popularity of psychoactive drugs, with lifetime experience of their use almost normalised as behaviour. A recent study of 3000 second year University students in the UK reported that over 50 % reported lifetime use of cannabis, with a third having used other drugs such as LSD or ecstasy (Webb et al. 1996). Although historically demonised by society, the true image of the average consumer of illicit substances is more benign. Drug policies driven by political will and social expectancies have compounded significantly the harm associated with their use.

Polydrug users and alcohol

While simultaneous polysubstance use is a common phenomenon among non-alcoholic populations, alcohol is most commonly one of the substances used in combination with other drugs, discounting tobacco (Barrett et al. 2006). The authors of this article recruited 149 drug-using university students to complete structured interviews about their use of various substances. For each substance ever used, participants provided details about the type, order and amount of all substances co-administered during its most recent administration. Alcohol, tobacco and cannabis were frequently taken with each other and with all other substances. Chi-squared tests revealed that when alcohol was consumed in combination with any of cannabis, psilocybin, MDMA, cocaine, amphetamines, or the prescription stimulant drug methylphenidate ($p < 0.01$) or LSD ($p < 0.05$), alcohol use preceded the administration of the other substance. Paired samples t-tests revealed that when alcohol was used with cocaine ($p < 0.01$) or the stimulant, methylphenidate, ($p < 0.05$) it was ingested in greater quantities than when used in their absence. Patterns of cannabis use were not systematically related to other substances. Tobacco use was demonstrated to increase relative to 'straight/sober' smoking rates when used with alcohol, cannabis, psilocybin, MDMA, cocaine, amphetamine ($p < 0.001$), LSD ($p < 0.01$) or methylphenidate ($p < 0.05$).

An earlier study of 3075 UK university students (Webb et al. 1996) showed that while 11% were non-drinkers, 61% of men and 48% of the women exceeded recommended limits of 14 units per week for women and 21 for men. Hazardous drinking (> 36 units per week for women, > 51 for men) was reported by 15% of the drinkers. Binge drinking was declared by 28% of drinkers. 60% of the men and 55% of the women reported having used cannabis once or twice and 20% of the sample reported regular cannabis use (weekly or more often). Experience with other illicit drugs was reported by 33% of the sample, most commonly LSD (lysergic acid diethylamide), amphetamines, ecstasy, and amyl nitrate which had each been used by 13-18% of students, and 34% of these had used several drugs.

Problem drinkers and polydrug use

Studying polydrug use among problem drinkers, Martin et al (1996) found that a majority (61%) of their 212 subjects reported simultaneous polydrug use (SPU) during the assessment interval of 120 days prior to admission for treatment, using Timeline Follow-back. Subjects who reported SPU were disproportionately younger, male, and unmarried, compared with those who did not report such use.

The most common alcohol/drug combinations were alcohol with cocaine (60% of subjects who reported SPU), alcohol with marijuana (51% of SPU subjects), and alcohol with sedatives (31% of SPU subjects). The most common three-drug combination was alcohol, cocaine, and marijuana (23% of SPU subjects). Alcohol use and drug use were associated at the event level, significantly more than associations predicted by the base rates of the individual behaviours. Their results suggest that polydrug use is an important focus for assessment and intervention in alcohol treatment programs.

Population studies

One US study examined rates of remission from substance-use disorders based on type of disorder (abuse vs. dependence), type of substance (alcohol vs. other drug), and polysubstance involvement (alcohol or drug vs. alcohol and drug) (Karno et al. 2008). Participants in the National Epidemiologic Survey on Alcohol and Related Conditions were included if they met criteria for a prior-to-past-year alcohol- and/ or drug-use disorder (n = 12,297). Odds ratios were computed to examine differences in the rate of remission as of the past year. Individuals with a diagnosis of alcohol misuse (as opposed to dependence) were more likely to have recovered than dependent drinkers. Individuals with both alcohol- and drug-use disorders were less likely to have recovered, compared with those with only one substance disorder. No differences were observed in remission rates between those with an alcohol-use disorder and those with a drug-use disorder. These findings support prior research in suggesting a worse prognosis for individuals with a diagnosis of dependence and problematic use of both alcohol and drugs.

The 1997 National Survey of Mental Health and Well-Being in Australia (Degenhardt et al. 2003) showed that alcohol use was related strongly to the use of other substances. Those who did not report alcohol use within the past 12 months were less likely to report using tobacco, cannabis, sedatives, stimulants or opiates. Higher rates again were observed among those with alcohol use disorders: half (51%) of those who were alcohol-dependent were regular tobacco smokers, one-third had used cannabis (32%); 15% reported other drug use; 15% met criteria for a cannabis use disorder and 7% met criteria for another drug use disorder.

Also in Australia, Degenhardt's paper about GHB and ketamine use, derived from a subsection of respondents (aged 14-39 years only) to the 2004 Australian Household Drug Survey (Australian Institute of Health and Welfare 2005), supplies some information about other drug use. While the prevalence of GHB and ketamine use was quite low, they found high rates of polydrug use among illicit drug users (Degenhardt and Dunn 2008). The most commonly used drug was alcohol, used by 95% of the total surveyed population (n = 11,595), with 28% of the total consuming more than 11 drinks in one day in the previous year, and 49% of 115 GHB-users and 57% of ketamine-users consuming 11 drinks or more in one day in the previous year. This may suggest either that use of GHB or ketamine lowers personal resistance to drinking alcohol, or conversely it opposes its effects (thereby reducing intoxication, as do amphetamines, for example). However, no evidence is available on this aspect.

Comorbidities and cognitive impairment

The comorbidities most commonly associated with polysubstance use, as demonstrated in at least one study (Skinstad and Swain 2001) include anxiety and mood disorders, followed by personality disorders. However, cognitive deficits are the characteristics most often associated with alcohol dependence.

Cognitive deficits were assessed in one study of dependent alcoholics (Durazzo et al. 2008). The goal of Durazzo's study was to investigate the influence of several common co-morbid medical conditions (primarily hypertension and hepatitis C), psychiatric (primarily unipolar mood and anxiety disorders), and substance use (primarily psychostimulant and cannabis) disorders, and chronic cigarette smoking on the neurocognitive functioning in short-term abstinent, treatment-seeking individuals with an alcohol use disorder. Seventy-five alcohol-dependent participants (average 51 years; 72 male) completed comprehensive neurocognitive testing after approximately 1 month of abstinence. Smoking status (smoker/nonsmoker) and age were significant independent predictors of cognitive efficiency, general intelligence, postural stability, processing speed, and visuospatial memory after adjustment for age norms and also controlling for estimated verbal intelligence, education, alcohol consumption, and medical, psychiatric, and substance-misuse co-morbidities. Results indicated that chronic smoking accounted for a significant portion of the variance in the neurocognitive performance of this cohort.

Several tests of visuospatial cognition are also known to be sensitive to chronic alcohol abuse. Beatty et al (1997) examined spatial cognition in a sample of 94 alcohol-dependent people, compared to controls, and looked for any influences on effects resulting from the use of other drugs. Groups that had misused only alcohol, alcohol and marijuana, or alcohol and multiple other drugs (A/P) were compared to the controls recruited from the community. Testing occurred after at least 3 weeks of treatment for the drug abusers. On all measures of visuospatial perception and construction, and on all measures of visuospatial learning and memory, all groups of alcoholics were impaired relative to controls, but there were no significant differences among the groups that misused alcohol. By contrast, on all measures of geographical knowledge that required more detailed place localisation, subjects in the A/P group were impaired, while subjects who misused only alcohol or alcohol and marijuana performed as well as controls. Their results seem to indicate that alcohol is the most disabling substance, and those who also use cannabis and other drugs have no more impairments than those associated with their alcohol use.

Another study of polydrug users tested for associated cognitive deficits (Nixon et al. 1998). Healthy control subjects (n=63) were compared with 40 individuals who misused alcohol only, 24 individuals who misused alcohol and stimulants, 16 individuals who misused alcohol and marijuana, and 41 individuals who misused alcohol and depressants/narcotics, or alcohol and two or more other drugs. All subjects were administered tests of short-term memory, spatial orientation, visual-spatial perception, and problem-solving. Results from the study indicated that control subjects and individuals who misused both alcohol and marijuana performed significantly better than the other groups on most tests. Gender was not significant. These results were not attributable to differences on measures of affect, or the years of chronic alcohol consumption.

Summary

The above studies all indicate that any assessment of alcohol use or misuse should include questioning on the use of other drugs. This should be taken into account as they can adversely influence the outcome of treatment.

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