REVIEW ARTICLE

Drugs 2006; 66 (9): 1229-1237
0012-6667/06/0009-1229/$44.95/0

Pharmacotherapy of Alcoholism in Patients with Co-morbid Psychiatric Disorders

Benjamin I. Goldstein,[1] *Artemis Diamantouros*,[1,2] *Ayal Schaffer*[1] and *Claudio A. Naranjo*[1,2]

1 Department of Psychiatry, Sunnybrook and Women's College Health Sciences Centre, University of Toronto, Toronto, Canada
2 Psychopharmacology Research Program, Sunnybrook and Women's College Health Sciences Centre, University of Toronto, Toronto, Canada

Contents

Abstract

There has been an exponential increase in recent years of literature pertaining to the treatment of individuals with alcohol use disorders and co-morbid psychiatric disorders. Patients with mood and anxiety disorders in particular have a very high prevalence of alcoholism. Alcoholism confers significant morbid risks to patients with psychiatric disorders, and vice versa, including markedly increased risk of suicide. Only recently have studies examined the impact of various psychiatric medications on alcohol use among patients with these disorders. Evidence supporting the benefits of antidepressants for co-morbid alcoholism and depression continues to mount. Although these studies have demonstrated benefits in terms of quantitative decreases in the volume and frequency of consumption, the benefits in terms of remission from alcoholism have yet to be shown conclusively.

The first randomised, controlled trial involving subjects with co-morbid alcoholism and bipolar disorder was recently conducted, yielding promising results for valproate in this population. The literature regarding co-morbid alcoholism and anxiety disorders has also seen recent progress, particularly in the study of post-traumatic stress disorder (PTSD). A placebo-controlled study of sertraline suggests some benefit in terms of alcohol use among individuals with early-onset PTSD and less severe alcohol dependence. Atypical antipsychotics such as

olanzapine and quetipaine have been examined in several open studies of subjects with alcoholism co-morbid with a variety of psychiatric conditions including bipolar disorder, PTSD and schizophrenia. This paper selectively reviews the evidence that is currently available for the pharmacological management of alcoholism among persons with co-morbid psychiatric illness. Effectiveness, safety and tolerability are considered, and directions for future study are discussed.

The prevalence of co-morbid psychiatric disorders among individuals with alcoholism is markedly increased compared with the general population.[1-3] Similarly, there is an increased prevalence of alcohol use disorders (AUD) among individuals with mood disorders, anxiety disorders, personality disorders and other psychiatric conditions. Patients with alcoholism and psychiatric co-morbidity are more likely to seek treatment for their alcoholism than alcoholic individuals without other psychiatric disorders,[4] and psychiatric patients with AUD or other substance abuse disorders visit hospital emergency departments significantly more frequently than psychiatric patients without AUD.[5]

A recent epidemiological study confirmed that individuals with co-morbid psychiatric disorders and AUD are more likely to utilise mental health services than individuals with AUD alone or psychiatric disorders alone.[6] The treatment costs of this co-morbid population have been estimated to be 60% greater than among individuals with psychiatric illness alone.[7] Unfortunately, individuals with co-morbid disorders are reported to have lower treatment adherence[8] and increased morbidity and mortality, including exceedingly high rates of suicidality.[9]

The recent National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a National Institute of Alcoholism and Alcohol Abuse (NIAAA) initiative, included a rigorous examination of the status of psychiatric disorders as independent versus secondary to AUD. The findings indicate that <1% of individuals who meet diagnostic criteria for a mood or anxiety disorder only have mood/anxiety episodes in the context of alcohol use. Among those with co-morbidity, the mood or anxiety disorder generally either persists despite abstinence from alcohol, can be shown to precede the AUD, or occurs episodically in the absence of active AUD.[3] In essence, individuals with psychiatric-AUD co-morbidity truly have dual diagnoses. Although common practice in the past was to advise abstinence and withhold psychiatric treatment pending the resolution or attenuation of alcoholism, the studies reviewed in this article indicate that the contemporary standard of treatment for AUD co-morbidity with psychiatric disorders is to treat both conditions simultaneously.

General principles of treatment for alcoholism in individuals without a co-morbid psychiatric condition apply equally in the co-morbid population. Initial treatment strategies consist of detoxification, pharmacological management of acute withdrawal symptoms, and a combination of pharmacological and psychosocial strategies aimed at either achieving and maintaining abstinence or maximising harm reduction. However, there are a number of ways in which psychiatric disorders may preclude optimal treatment outcomes. Psychiatric illnesses render pervasive effects on perception, insight, judgement and behaviour, each of which can compromise treatment outcomes. For instance, a patient with acute depression may not have the motivation or concentration to be able to adhere reliably to complex medication regimens or to attend self-help groups for alcoholism. A patient with panic disorder and agoraphobia may be unlikely to attend an alcoholism treatment clinic for fear of triggering a series of panic attacks. An antisocial patient can engender strong negative emotional reactions in healthcare providers, which may limit opportunities for ongoing care.

Given these specific impairments, it is important to consider psychiatric co-morbidity in any alcohol-

ism treatment plan. Key characteristics of the ideal medication for treating AUD with co-morbid psychiatric illness that have been proposed include (i) relief of psychiatric symptoms; (ii) decreased alcohol use by either relieving withdrawal symptoms or lessening craving; (iii) enhanced relapse prevention; (iv) low abuse liability; (v) infrequent dose administration; and (vi) good tolerability.[10] This article reviews the current evidence for pharmacological treatment of AUD among individuals with co-morbid psychiatric disorders, including specific targeted strategies, and pharmacological and clinical considerations. Not all of the studies include data regarding the six criteria listed above; however, information relating to these criteria is provided where possible.

1. Major Depressive Disorder

There is a reciprocal association between AUD and major depressive disorder (MDD), such that each has a higher prevalence when the other is present. Recent epidemiological data indicate that 12-month prevalence of MDD is more than doubled (odds ratio 2.3, 95% CI 2.3, 2.9) among those with AUD compared with non-AUD individuals.[3] This corroborates previous estimates of a 2- to 4-fold increase in the prevalence of MDD among those with AUD.[2,11] Only 5.8% of individuals with a 12-month AUD seek treatment for their AUD during that time,[3] and of these treatment-seeking individuals, one-third have MDD.

Co-morbid AUD is known to adversely affect the burden of depressive illness. Studies of both clinical and community samples have shown that depressed patients with AUD experience increased severity of depression, increased suicidality[9,12] and poorer outcomes.[13,14] Alcoholic individuals with co-morbid MDD are also more likely to experience relapse of alcohol use.[15]

Of all the psychiatric disorders that co-occur with alcoholism, depression is the most researched. In studies of severely depressed alcoholic patients, benefits with respect to decreasing alcohol use have been reported with desipramine,[16] imipramine,[17] fluoxetine[18] and sertraline.[19,20] As a general principle, among the antidepressants, selective serotonin reuptake inhibitors (SSRIs), e.g. fluoxetine and sertraline, have a more favourable adverse-effect profile than tricyclic antidepressants (TCAs), e.g. desipramine and imipramine, and show minimal risk of lethality when taken in overdose. Worthy of note is that serum TCA concentrations at a fixed medication dose are lower among depressed alcoholic patients than among depressed patients who are not alcoholic, suggesting that serum concentrations in this population may require closer monitoring and that drug doses may need to be increased.[21] This is likely to be due to the impact of heavy alcohol use on hepatic metabolism.

A recent rigorous meta-analysis showed that treatment studies of co-morbid depression and alcoholism with depression effect sizes >0.5 demonstrated benefits over placebo in terms of quantity of alcohol use.[22] Of the 44 placebo-controlled trials identified, 14 studies were included in the meta-analysis. The combined data showed persistent abstinence during treatment in 28.7% of subjects receiving active treatment versus 22.5% of those receiving placebo, for an approximate effect size of 0.35.[22] The results of several of these studies are described in this article.[16-18,20]

The SSRI sertraline has been studied in combination with cognitive-behavioural therapy (CBT).[20] Eighty-two subjects with depression and alcoholism were randomly assigned to 12 weeks of either sertraline or placebo as adjunctive treatment to CBT. Sertraline-treated subjects (mean dosage 186 mg/day) reported fewer drinks per drinking day than placebo-treated subjects, although the two groups were similar in terms of percentage of days abstinent. This study also found that decreased alcohol consumption was associated with a reduction in depressive symptoms.[20]

A randomised, placebo-controlled trial of nefazodone, a serotonin antagonist and reuptake inhibitor, for co-morbid alcoholism and depression was conducted recently.[23] Forty-one subjects were randomised to nefazodone (200–600 mg/day) or placebo, in addition to supportive psychotherapy. Nefazodone-treated subjects showed a significantly greater reduction in heavy drinking days and in total

drinks than placebo-treated subjects. Abstinence was achieved by 33% of nefazodone-treated subjects and 15% of placebo-treated subjects, although the sample was under-powered to identify significant differences in abstinence rates ($p = 0.19$).

Cornelius et al.[24] conducted a 12-week open-label study of fluoxetine for depressed adolescents with AUD. Fluoxetine-treated subjects demonstrated a significant decrease in the number of drinks per drinking day, and a trend towards decreased number of drinking days per week. While all subjects ($n = 13$) were deemed either "much" or "very much" improved with respect to depression on the Clinical Global Improvement measure, just over half of the sample showed this degree of improvement with respect to alcoholism. One-year follow-up data[25] shows that all of the subjects chose to discontinue fluoxetine within 3 months of naturalistic follow-up. At 1-year follow-up, subjects continued to appreciate persistent benefits in terms of frequency of drinking, although mean number of drinks per drinking day remained high (approximately five). Nonetheless, given the increased incidence of mania among those with early-onset[26] depression, it is especially important in this population to balance alcohol-related benefits with the risk of a polarity switch into mania.

The benefits of antidepressants in terms of attenuating alcohol consumption among individuals with depression may extend to those who do not have AUD. Goldstein et al.[27] reported significantly decreased frequency of alcohol consumption among depressed individuals treated in open-label fashion with desipramine. In a randomised, placebo-controlled study of fluoxetine 20 mg/day in alcoholic subjects with subthreshold symptoms of depression or anxiety, there was no significant benefit of treatment over placebo with respect to attenuating these symptoms.[28]

In addition to studies of antidepressants for individuals with concurrent MDD and alcoholism, there is some evidence supporting naltrexone use in this population. Salloum et al.[29] reported results from a pilot study of naltrexone showing that naltrexone add-on treatment resulted in decreased alcohol use as well as decreased depressive symptoms in a sample of 14 subjects whose alcoholism had not remitted with an SSRI alone.

2. Bipolar Disorder

Bipolar disorder shares the highest co-morbidity with AUD of all the major psychiatric disorders, with the lifetime prevalence of AUD approaching 50%.[1] Mood-stabilising medications are the mainstay of treatment for bipolar disorder. These include lithium, anticonvulsants such as valproate and lamotrigine, and atypical antipsychotics such as olanzapine, quetiapine and risperidone.

In a recent study, 59 subjects with alcoholism and bipolar disorder were randomly assigned to 24 weeks of valproate treatment (starting dosage 750 mg/day, titrated to therapeutic serum trough concentrations of 50–100 μg/L) or placebo as add-on to ongoing lithium carbonate treatment and psychosocial interventions.[30] Results from this study showed that the valproate group had significantly fewer heavy drinking days and a trend towards fewer drinks per heavy drinking day. When medication adherence was added as a co-variate, the treatment group showed significant benefits over placebo in terms of number of drinks per heavy drinking day and number of drinks per drinking day. In addition, mean γ-glutamyl transpeptidase (γ-GT) levels were lower in the valproate group.

There is case-report evidence that naltrexone use among women with co-morbid alcoholism and acute manic syndromes may be poorly tolerated, as its use in two patients was associated with intolerable symptoms of opiate withdrawal.[31] Gabapentin, a new anticonvulsant that is a structural analogue of GABA, has been used as an adjunctive treatment in patients with bipolar disorder. In a recent study of gabapentin for bipolar disorder ($n = 43$; mean dosage 1270 mg/day), alcoholism was the strongest predictor of response to treatment.[32] However, the study did not specifically address changes in alcohol craving or consumption.

Data from a 12-week pilot, open-label study of quetiapine ($n = 17$, mean dosage 239 mg/day) for co-morbid bipolar disorder and cocaine abuse

showed that, among subjects with alcohol craving at baseline, quetiapine was associated with reduced alcohol craving and fewer drinking days per week during treatment.[33] Alcohol craving was associated with symptoms of depression but not of mania.

Geller et al.[34] examined the effect of lithium treatment on the mood symptoms and substance dependency of 21 adolescents (mean age = 16.3 years) in a small, randomised, placebo-controlled trial. Eighty-five percent of the sample had AUD, either alone or in combination with a drug use disorder. Subjects in the lithium-treated group were more likely than those in the placebo group to demonstrate abstinence from substances, in addition to superior global assessment scores. Using a global assessment scale, 46% of the active treatment group were considered responders compared with 8% of the placebo group.

It should be noted that individuals with bipolar disorder and co-morbid substance use disorders, including AUD, may be at especially high risk of antidepressant-induced mania,[35] and despite the benefits these medications have shown in the treatment of depression with co-morbid AUD, their use in co-morbid bipolar disorder-AUD for the sole purpose of minimising alcohol consumption is not recommended.

3. Generalised Anxiety Disorder

Generalised anxiety disorder (GAD) is characterised by excessive anxiety and worry that is both pervasive (effects several domains of life) and chronic (minimum duration of 6 months).[36] Alcohol-dependent individuals have a 2-fold increased 12-month prevalence of GAD and individuals with GAD have a 4-fold increased risk of alcoholism compared with the general population.[3]

Although benzodiazepines are one of the mainstays of acute alcoholic detoxification and despite their efficacy in the treatment of anxiety, their addictive potential limits use as a maintenance pharmacotherapy in a concurrent-disorder population. Some 30 years ago, Kissin[37] recognised the special needs of individuals with co-morbid AUD and anxiety, and listed three criteria for an ideal anxiolytic for alcoholics: (i) it should be effective in minimising treatment withdrawal rates; (ii) it should have low abuse potential; and (iii) it should not potentiate the effects of alcohol.

The most studied psychotropic medication for the treatment of GAD with co-morbid alcoholism is buspirone, a partial serotonin agonist non-benzodiazepine anxiolytic.[38] Benefits of this medication include the absence of addiction potential and lack of additive effects on psychomotor coordination.[39] Several placebo-controlled trials of buspirone in the population have been conducted, with mixed results. One study of male veterans randomised to buspirone 45–60 mg/day or placebo failed to show significant between-group differences on any of the alcohol-related measures, including survival analyses and volumetric assessment.[40] Bruno[41] reported no benefit of buspirone over placebo on alcohol consumption. However, the buspirone-treated group reported significantly decreased alcohol craving, anxiety and depression compared with placebo. In a study with positive findings, Tollefson et al.[42] reported that treatment with buspirone led to decreased anxiety symptoms and number of days desiring alcohol, with greater retention rates and global improvement. A randomised, placebo-controlled trial involving 61 subjects with GAD and alcoholism conducted by Kranzler et al.[43] showed that buspirone is associated with greater treatment retention, delayed relapse to heavy drinking and fewer drinking days during follow-up. It is important to note that a delayed onset of action has been described, with maximum treatment effect between the second and fourth weeks of treatment.[43] Overall, the mixed results have led to limited use of buspirone for this indication. Studies of antidepressants such as SSRIs that have demonstrated efficacy in non-co-morbid GAD are needed in the co-morbid population.

4. Social Phobia

Social phobia is a disorder in which there is marked and persistent fear related to social situations, secondary to a fear of being scrutinised or humiliating oneself, and in which the individual

experiences significant anxiety or a panic attack if exposed to the situation.[36] Self-medication models of co-morbidity with AUDs have been suggested, and these argue that the socially anxious individual initiates alcohol consumption in the hope of relieving stress and continues this operant behaviour because of the strong negative reinforcement that occurs. Epidemiological and clinical studies alike show a strong bi-directional association between alcohol dependence and social phobia. The prevalence of alcoholism among individuals with social phobia is approximately 20%,[44] and individuals with alcoholism are four times more likely to have 12-month co-morbid social phobia than individuals without alcoholism.[3]

Randall et al.[45] conducted a randomised, double-blind pilot study of high-dose paroxetine (target dose 60 mg/day) versus placebo for co-morbid social phobia and alcoholism. The study was limited by a small sample size (n = 6 for paroxetine group, n = 9 for placebo group). However, subjects in the paroxetine group were significantly more likely to show clinician-rated improvement (50%) than subjects in the placebo group (11%). Although changes in quantity frequency measures of alcohol consumption were not significantly different between the paroxetine and placebo groups, treatment effect sizes were in the moderate range (eta^2 values 0.54–0.66). At a minimum, this suggests that further study of paroxetine and other SSRIs in the co-morbid social phobia-AUD population is worthwhile.

5. Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is an anxiety disorder that manifests in approximately 25% of individuals who experience a potentially life-threatening event.[36] Symptoms include re-experiencing, avoidance and autonomic hyper-arousal. PTSD is common among those with addiction, with a recent study reporting a lifetime prevalence >50%.[46] Similarly, alcoholism is common, with estimated prevalence of up to 68% among patients with trauma exposure or PTSD.[47] Some would argue that the high degree of co-morbidity is due to alcohol's amnestic properties, which blur the memories of the traumatic event(s).[48] Another theory is that alcoholism predisposes one to trauma exposure.[49] In truth, these are not mutually exclusive theories and reasons for the high degree of overlap are likely to be multifactorial.

Regardless of the putative reasons for co-morbidity, treatment of both disorders is clearly indicated in this population. Brady et al.[50] conducted a 12-week study of open treatment with sertraline for co-morbid PTSD and alcoholism. The results showed treatment benefits in terms of more days of abstinence and fewer drinks per day. However, a subsequent placebo-controlled trial showed mixed results. Although sertraline was superior to placebo among individuals with less severe alcohol dependence and early-onset PTSD, individuals with severe alcohol dependence and later-onset PTSD showed greater attenuation of alcohol consumption in response to placebo.[51]

Monnelly et al.[52] examined the use of the atypical antipsychotic quetiapine in a retrospective study of 50 patients with alcohol dependence, of whom 90% had co-morbid PTSD. The group that received quetiapine (n = 30, 25–200mg nightly) reported greater mean number of days abstinent than the control group that did not receive quetiapine, and the mean number of days to relapse approached significance (p = 0.07).

6. Panic Disorder

Panic disorder is associated with an approximately 3-fold greater prevalence of alcoholism.[1] A recent estimate of the prevalence of AUD in panic disorder is 15–19%.[3] Interestingly, the nature of the relationship between panic disorder and alcoholism may differ from other anxiety disorders. Studies have shown that AUD precedes panic disorder in the majority of patients.[53,54] As with other psychiatric disorders, co-morbidity with alcoholism is associated with increased illness severity and elevated risk of suicidality.[53]

To date, there are no large-scale or placebo-controlled studies with which to inform clinical decision making regarding the management of alco-

holism with co-morbid panic disorder. An open-label study of desipramine[55] and a case report of valproate[56] suggest a possible benefit from these medications, but replication is required. From a clinical perspective, the efficacy, tolerability and safety of SSRIs in both primary AUD and in panic disorder suggest that controlled trials in the co-morbid panic disorder-AUD population are indicated.

7. Schizophrenia

Schizophrenia, an illness characterised by delusions, hallucinations, disorganised speech and behaviour, and social and emotional withdrawal,[36] has a lifetime prevalence of approximately 1% and is associated with a 10-fold increased prevalence of AUD.[1] Littrell et al.[57] conducted a 12-month open-label trial of the atypical antipsychotic olanzapine in a sample of 30 schizophrenic patients with alcoholism and at least one other drug of abuse/dependence. Results of that study showed full remission from substance (including alcohol) use among 70% of subjects and early partial remission in the remaining 30%. However, it should be noted that there have been several case reports of pancreatitis associated with olanzapine treatment.[58,59] It is not yet known whether there is a synergistic effect of alcohol and olanzapine on the development of pancreatitis, whether this is a class effect among atypical antipsychotics, or if this is an incidental finding. In any event, the possibility of pancreatitis should be considered when gastrointestinal symptoms emerge during treatment with olanzapine or other atypical antipsychotics.

In another recent study, 31 individuals with schizophrenia were randomised to receive either naltrexone or placebo in addition to their antipsychotic medication and a weekly psychosocial intervention.[60] Naltrexone-treated patients had significantly fewer drinking days and heavy drinking days, and greater attenuation in craving compared with patients who received placebo. Importantly, naltrexone was well tolerated, as evidenced by a lack of a significant difference in adverse effects compared with placebo.

Non-adherence to treatment in schizophrenia is a common problem. Flupentixol is a typical antipsychotic medication that can be delivered in an intramuscular depot formulation to help ameliorate this problem. A recent open-label study of flupentixol (10–60mg intramuscularly) was conducted with 27 schizophrenic patients with co-morbid alcoholism.[61] Among the 21 subjects who entered the intention-to-treat analysis, flupentixol treatment resulted in significant reduction of alcohol consumption compared with baseline. However, as in the non-co-morbid population, the increased risk of tardive dyskinesia and other adverse neurological effects must be weighed against any potential benefits of using typical antipsychotics. In another uncontrolled, retrospective study of schizophrenic patients, treatment with clozapine was associated with greater rates of abstinence from alcohol and cannabis (54%) than treatment with risperidone (13%),[62] replicating an earlier report that clozapine is associated with decreased severity of alcohol abuse and fewer drinking days.[63] Given the risk of agranulocytosis during treatment with clozapine, strict adherence to haematological monitoring protocols is required. A recent case report yielded preliminary evidence for treatment with the atypical antipsychotic aripiprazole (a novel agent with dopamine partial agonist effects), which resulted in both attenuated alcohol consumption and alcohol craving.[64] Clearly, randomised, placebo-controlled studies of medications with potential benefit for co-morbid AUD and schizophrenia are needed.

8. Conclusion

The literature regarding co-morbid psychiatric disorders and AUD has increased significantly in recent years. Nonetheless, further study of treatments for this population is urgently needed for the following reasons. First, there are psychiatric conditions that have not been studied at all with respect to AUD, including several personality disorders, obsessive-compulsive disorder, attention-deficit hyperactivity disorder and impulse-control disorders. Secondly, there are several specific psychiatric medications that may have benefits with respect to

minimising alcohol consumption in co-morbid populations, but which have not yet been studied rigorously, including gabapentin, lamotrigine and bupropion. Thirdly, for those medications that have been studied, randomised, controlled trials are needed to rigorously assess benefits versus placebo. To this end, there is a need for greater consistency between studies in the measures used to quantify alcohol use. Finally, future studies are needed to address the potential benefits of psychosocial interventions, either in comparison with or in addition to medications. Individuals with psychiatric illness who also have AUD are generally excluded from clinical trials and, although there is some movement towards including these co-morbid patients, more data are urgently needed.

Acknowledgements

The authors received no funding for the preparation of this article and have no conflicts of interest directly relevant to its contents.

References

1. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. JAMA 1990; 264: 2511-8
2. Kessler RC, Crum RM, Warner LA, et al. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry 1997; 54: 313-21
3. Grant BF, Stinson FS, Dawson DA, et al. Co-occurrence of 12-month alcohol and drug use disorders and personality disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry 2004; 61: 361-8
4. Wu LT, Ringwalt CL, Williams CE. Use of substance abuse treatment services by persons with mental health and substance use problems. Psychiatr Serv 2003; 54: 363-9
5. Curran GM, Sullivan G, Williams K, et al. Emergency department use of persons with comorbid psychiatric and substance use disorders. Ann Emerg Med 2003; 41: 659-67
6. Wu LT, Kouzis AC, Leaf PJ. Influence of comorbid alcohol and psychiatric disorders on utilization of mental health services in the National Comorbidity Survey. Am J Psychiatry 1999; 156: 1230-6
7. Dickey B, Azeni H. Persons with dual diagnoses of substance abuse and major mental illness: their excess costs of psychiatric care. Am J Public Health 1996; 86: 973-7
8. Woody G. The challenge of dual diagnosis. Alcohol Res Health 1996; 20: 76-80
9. Cornelius JR, Salloum IM, Mezzich J, et al. Disproportionate suicidality in patients with comorbid major depression and alcoholism. Am J Psychiatry 1995; 152: 358-64
10. Kosten TR, Kosten TA. New medication strategies for comorbid substance use and bipolar affective disorders. Biol Psychiatry 2004; 56: 771-7
11. Grant BF, Harford TC. Comorbidity between DSM-IV alcohol use disorders and major depression: results of a national survey. Drug Alcohol Depend 1995; 39: 197-206
12. McCloud A, Barnaby B, Omu N, et al. Relationship between alcohol use disorders and suicidality in a psychiatric population. Br J Psychiatry 2004; 184: 439-45
13. Hasin DS, Tsai WY, Endicott J, et al. Five-year course of major depression: effects of comorbid alcoholism. J Affect Disord 1996; 41: 63-70
14. Rae AM, Joyce PR, Luty SE, et al. The effect of a history of alcohol dependence in adult major depression. J Affect Disord 2002; 70: 281-90
15. Greenfield SF, Weiss RD, Muenz LR, et al. The effect of depression on return to drinking: a prospective study. Arch Gen Psychiatry 1998; 55: 259-65
16. Mason BJ, Kocsis JH, Ritvo EC, et al. A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. JAMA 1996; 275: 761-7
17. McGrath PJ, Nunes EV, Stewart JW, et al. Imipramine treatment of alcoholics with primary depression. Arch Gen Psychiatry 1996; 53: 232-40
18. Cornelius JR, Salloum IM, Ehler JG, et al. Fluoxetine in depressed alcoholics: a double-blind, placebo-controlled trial. Arch Gen Psychiatry 1997; 54: 700-5
19. Roy A. Placebo-controlled study of sertraline in depressed recently abstinent alcoholics. Biol Psychiatry 1998; 44: 633-7
20. Moak DH, Anton RF, Latham PK, et al. Sertraline and cognitive behavioral therapy for depressed alcoholics: results of a placebo-controlled trial. J Clin Psychopharmacol 2003; 23: 553-662
21. Ciraulo DA, Alderson LM, Chapron DJ, et al. Imipramine disposition in alcoholics. J Clin Psychopharmacol 1982; 2: 2-7
22. Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence. JAMA 2004; 291: 1887-96
23. Hernandez-Avila CA, Modesto-Lowe V, Feinn R, et al. Nefazodone treatment of comorbid alcohol dependence and major depression. Alcohol Clin Exp Res 2004; 3: 433-40
24. Cornelius JR, Bukstein OG, Birmaher B, et al. Fluoxetine in adolescents with major depression and an alcohol use disorder: an open-label trial. Addict Behav 2001; 26: 735-9
25. Cornelius JR, Bukstein OG, Salloum IM, et al. Fluoxetine in depressed AUD adolescents: a 1-year follow-up evaluation. J Child Adolesc Psychopharmacol 2004; 14: 33-8
26. Geller B, Zimerman B, Williams M, et al. Bipolar disorder at prospective follow-up of adults who had a prepubertal major depressive disorder. Am J Psychiatry 2001; 158: 125-7
27. Goldstein BI, Schaffer A, Levitt A, et al. Depressive symptoms and alcohol consumption among non-alcoholic depression patients treated with desipramine. Can J Psychiatry 2004; 49: 859-62
28. Janiri L, Gobbi G, Mannelli P, et al. Effects of fluoxetine at antidepressant doses on short-term outcome of detoxified alcoholics. Int Clin Psychopharmacol 1996; 11: 109-17
29. Salloum IM, Cornelius JR, Thase ME, et al. Naltrexone utility in depressed alcoholics. Psychopharmacol Bull 1998; 34: 111-5
30. Salloum IM, Cornelius JR, Daley DC, et al. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism. Arch Gen Psychiatry 2005; 62: 37-45

31. Sonne SC, Brady KT. Naltrexone for individuals with comorbid bipolar disorder and alcohol dependence. J Clin Psychopharmacol 2000; 20: 114-5
32. Perugi G, Toni C, Frare F, et al. Effectiveness of adjunctive gabapentin in resistant bipolar disorder: is it due to anxious-alcohol abuse comorbidity? J Clin Psychopharmacol 2002; 22: 584-91
33. Longoria J, Brown ES, Perantie DC, et al. Quetiapine for alcohol use and craving in bipolar disorder. J Clin Psychopharmacol 2004; 24: 101-2
34. Geller B, Cooper TB, Sun K, et al. Double blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. J Am Acad Child Adolesc 1998; 37: 171-8
35. Goldberg JF, Whiteside JE. The association between substance abuse and antidepressant-induced mania in bipolar disorder: a preliminary study. J Clin Psychiatry 2002; 63: 791-5
36. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington DC: American Psychiatric Association, 1994
37. Kissin B. The use of psychoactive drugs in the long-term treatment of chronic alcoholics. Ann N Y Acad Sci 1975; 252: 385-95
38. Kranzler HR. Evaluation and treatment of anxiety symptoms and disorders in alcoholics. J Clin Psychiatry 1996; 57 Suppl. 7: 15-21
39. Modesto-Lowe V, Kranzler HR. Diagnosis and treatment of alcohol-dependent patients with comorbid psychiatric disorders. Alcohol Res Health 1999; 23: 144-9
40. Malcolm R, Anton RF, Randall CL, et al. A placebo-controlled trial of buspirone in anxious inpatient alcoholics. Alcohol Clin Exp Res 1992; 16: 1007-13
41. Bruno F. Buspirone in the treatment of alcoholic patients. Psychopathology 1989; 22 Suppl. 1: 49-59
42. Tollefson GD, Montague-Clouse J, Tollefson SL. Treatment of comorbid generalized anxiety in a recently detoxified alcoholic population with a selective serotonergic drug (buspirone). J Clin Psychopharmacol 1992; 12: 19-26
43. Kranzler HR, Burleson JA, Del Boca FK, et al. Buspirone treatment of anxious alcoholics. Arch Gen Psychiatry 1994; 51: 720-31
44. Lepine JP, Pelissolo A. Social phobia and alcoholism: a complex relationship. J Affect Disord 1998; 50 Suppl. 6: 33-7
45. Randall CL, Johnson MR, Thevos AK, et al. Paroxetine for social anxiety and alcohol use in dual-diagnosed patients. Depress Anxiety 2001; 14: 255-62
46. Reynolds M, Mezey G, Chapman M, et al. Co-morbid post-traumatic stress disorder in a substance misusing clinical population. Drug Alc Dep 2005; 77: 251-8
47. Riggs DS, Rukstalis M, Volpicelli JR, et al. Demographic and social adjustment characteristics of patients with comorbid posttraumatic stress disorder and alcohol dependence: potential pitfalls to PTSD treatment. Addict Behav 2003; 28: 717-30
48. Stewart SH, Pihl RO, Conrod P, et al. Functional association among trauma PTSD and substance-related disorders. Addict Behav 1998; 23: 797-812
49. Chilcoat HD, Breslau N. Post-traumatic stress disorder and drug disorders: testing causal pathways. Arch Gen Psychiatry 1998; 55: 913-7
50. Brady KT, Sonne SC, Roberts JM. Sertraline treatment of comorbid posttraumatic stress disorder and alcohol dependence. J Clin Psychiatry 1995; 56: 502-5
51. Brady KT, Sonne S, Anton RF, et al. Sertraline in the treatment of comorbid alcohol dependence and posttraumatic stress disorder. Alcohol Clin Exp Res 2005; 29: 395-401
52. Monnelly EP, Ciraulo DA, Knapp C, et al. Quetiapine for treatment of alcohol dependence. J Clin Psychopharmacol 2004; 24: 532-5
53. Sequi J, Marquez M, Canet J, et al. Panic disorder in a Spanish sample of 89 patients with pure alcohol dependence. Drug Alcohol Depend 2001; 63: 117-21
54. Katerndahl DA, Realini JP. Relationship between substance abuse and panic attacks. Addict Behav 1999; 24: 731-6
55. Nunes EV, McGrath PJ, Quitkin FM, et al. Imipramine treatment of alcoholism with comorbid depression. Am J Psychiatry 1993; 150: 963-5
56. Brady KT, Sonne S, Lydiard RB. Valproate treatment of comorbid panic disorder and affective disorders in two alcoholic patients. J Clin Psychopharmacol 1994; 14: 81-2
57. Littrell KH, Petty RG, Hilligoss NM, et al. Olanzapine treatment for patients with schizophrenia and substance abuse. J Subst Abuse Treat 2001; 21: 217-21
58. Hagger R, Brown C, Hurley P. Olanzapine and pancreatitis. Br J Psychiatry 2000; 177: 567
59. Doucette DE, Grenier JP, Robertson PS. Olanzapine-induced acute pancreatitis. Ann Pharmacother 2000; 34: 1128-31
60. Petrakis IL, O'Malley S, Rounsaville B, et al. Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia. Psychopharmacology (Berl) 2004; 172: 291-7
61. Soyka M, Aichmuller C, vBardeleben U, et al. Flupenthixol in relapse prevention in schizophrenics with comorbid alcoholism: results from an open clinical study. Eur Addict Res 2003; 9: 65-72
62. Green AI, Burgess ES, Dawson R, et al. Alcohol and cannabis use in schizophrenia: effects of clozapine vs risperidone. Schizophr Res 2003; 60: 81-5
63. Drake RE, Xie H, McHugo GH, et al. The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. Schizophr Bull 2000; 26: 441-9
64. Warsi M, Sattar SP, Bhatia SC, et al. Aripiprazole reduces alcohol use. Can J Psychiatry 2005; 50: 244

Correspondence and offprints: Dr *Ayal Schaffer*, Mood Disorders Program, Department of Psychiatry, Sunnybrook and Women's College Health Sciences Centre, 2075 Bayview Avenue, Toronto, M4N 3M5, Canada.
E-mail: ayal.schaffer@sunnybrook.ca