

**The Prevalence and Impact of Alcohol Problems in Major Depression:
A Systematic Review**

Lynn E. Sullivan, M.D., David A. Fiellin, M.D., and Patrick G. O'Connor, M.D., M.P.H

From the Department of Internal Medicine
Yale University School of Medicine, New Haven, CT

Correspondence to: Lynn E. Sullivan, M.D., Yale University School of Medicine,
333 Cedar St., P.O. Box 208025, New Haven, CT 06520-8025.

Telephone: (203) 688-9105 Fax: (203) 688-4092 email: lynn.sullivan@yale.edu

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ABSTRACT

Major depression and alcohol problems are common in primary care, yet little is known about the prevalence of alcohol problems in patients with depression or alcohol's effect on depression outcomes. We strove to answer 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 healthcare utilization, and in which alcohol categories and treatment settings have patients with depression and alcohol problems been evaluated? English language studies from MEDLINE, PsychINFO, and Cochrane Controlled Trial Registry were reviewed. Studies were selected using predefined criteria if they reported on the prevalence or effects of alcohol problems in depression. Thirty-five studies met criteria and revealed a median prevalence of current or lifetime alcohol problems in depression of 16% (range=5-67%) and 30% (range=10-60%), respectively. This compares to 7% for current and 16 to 24% for lifetime alcohol problems in the general population. There is evidence that antidepressants improve depression outcomes in persons with alcohol dependence. Alcohol problems are associated with worse outcomes with respect to depression course, suicide/death risk, social functioning, and healthcare utilization. The majority of the studies, 34 of 35 (97%), evaluated alcohol abuse and/or dependence, and 25 of 35 (71%) were conducted in psychiatric inpatients. We conclude that alcohol problems are more common in depression than in the general population, are associated with adverse clinical and health care utilization outcomes, and that antidepressants can be effective in the presence of alcohol dependence. In addition, the literature focuses almost exclusively on patients with alcohol abuse and/or dependence in psychiatric inpatient settings, and excludes patients with less severe alcohol problems and primary care outpatient settings.

Major depression affects approximately 9.9 million Americans [1] or roughly 5% of the population, and is the leading cause of disability in the United States [2]. The prevalence of depression ranges from 5 to 9% in primary care [3, 4] and between 40 and 60% of depression treatment occurs in this setting [5-8]. From the mid-1980s through the mid-1990s, visits to primary care for depression doubled and the proportion of antidepressant prescriptions written by primary care providers increased from 41 to 48% [9].

Similarly, alcohol problems including at-risk drinking, alcohol abuse, and alcohol dependence are highly prevalent [10-12]. The National Institute of Alcohol Abuse and Alcoholism reported a prevalence for alcohol abuse and dependence of 7% in 1992 [13]. In one primary care-based study of 19372 adults, less severe alcohol problems such as at-risk drinking were identified in 19.7% [14] while, in population-based studies, hazardous drinking ranged from 18 to 24% [15, 16] and harmful drinking from 0.3 to 14% [17, 18].

Patients with depression frequently have alcohol problems. One household survey reported a prevalence of 16% for any alcohol diagnosis in depressed patients [19]. These conditions have been found to coexist in diverse age, sex, and racial groups [20-23]. Alcohol problems in depressed patients presents diagnostic and management challenges and may adversely affect the course of depression and its response to standard therapies. Therefore, this systematic review was undertaken to 1) determine the prevalence of alcohol problems in patients with depression, 2) evaluate alcohol's effects on health-related outcomes, and 3) determine the alcohol categories and treatment settings addressed in these studies. In addition, we assessed the methodologic quality of the literature.

This review addresses the following clinical questions: How common are alcohol problems in patients with depression? Will a patient's depression course and response to antidepressant therapy be affected by alcohol problems? Do alcohol problems affect the risk of suicide/death in patients with depression? How do alcohol problems impact the social functioning and healthcare utilization of depressed patients? In which alcohol categories and treatment settings have patients with depression and alcohol problems been evaluated?

Methods

Search Strategy

We identified English language studies by searching the following databases: MEDLINE (1980 to September 2002), PsychINFO (1984 to September 2002), and the Cochrane Central Register of Controlled Trials (through 4th quarter of year 2002). Specific Medical Subject Headings and text words in MEDLINE are listed in Table 1.

Publications were limited to clinical trials, consensus development conferences, editorials, guidelines, journal articles, meta-analyses, multi-center studies, reviews, twin studies, and validation studies.

Using a similar search strategy, we reviewed the Cochrane Database of Systematic Reviews using alcohol and depression in the title or as keywords, and accessed the Cochrane Depression, Anxiety, and Neurosis Group and Cochrane Drugs and Alcohol Group.

Inclusion Criteria

Studies were included if they met the following five criteria: 1) adult sample (≥ 19 years old for MEDLINE, ≥ 18 years old for PsychINFO); 2) current major depression (not “depressive symptoms” or dysthymia) according to standard or operationally defined criteria; 3) current (past year) or lifetime alcohol problem or use; 4) no polysubstance abuse; and 5) data offered on the prevalence of alcohol problems or use in depression and/or their relationship to depression-related outcomes.

Two reviewers independently applied these criteria to all abstracts. One hundred abstracts were randomly selected to determine a simple kappa statistic of 0.66, indicating fair to good agreement between the reviewers [24]. When inclusion criteria were unclear from the abstract, the article was reviewed. In the 43/1579 (3%) cases of discordant readings, final inclusion/exclusion was determined by consensus between the two reviewers upon review of the manuscript. Selected bibliographies were reviewed for additional manuscripts.

Data Extraction

The following data were extracted by one of two reviewers: treatment setting, demographics, alcohol problem or use category (Table 2), diagnostic tools used for depression, prevalence of depression, prevalence of alcohol problems or use, prevalence of alcohol problems or use in depression, and descriptions of interventions and outcomes. We categorized these studies of patients with current depression according to either current or lifetime alcohol problems or use, or both. Because of concordance between the diagnosis of alcoholism according to Research Diagnostic Criteria and Feighner criteria with the definitions of alcohol abuse and dependence found in the Diagnostic and Statistical Manual [25], we combined studies addressing alcoholism, [26-29] alcohol

abuse, and dependence. Similarly, research has demonstrated agreement between International Statistical Classification of Disease and Related Health Problems and Diagnostic and Statistical Manual criteria for alcohol dependence [30] so we combined studies using these criteria. When reported, quantitative data including appropriate statistical test results for outcomes were extracted.

Quality of Evidence

Randomized clinical trials

Using a standard quality checklist [31], two reviewers independently evaluated the quality of the randomized clinical trials. This 5-point checklist addresses the quality of randomization, blinding, and the handling of patients who withdraw or drop out of the study. According to this scoring system, articles with a score of 0-2 are considered poor quality and articles with a score of 3-5 are considered excellent quality. Differences between reviewers were resolved by consensus.

Observational studies

Two reviewers independently evaluated the observational cohort studies, cross-sectional studies, and case series, and assigned a Quality Index score [32]. Despite the utility of observational methods for determining prognosis in health [33, 34], there are few instruments to evaluate the quality of observational studies and little consensus regarding quality measures. We used a 31-point scale that assessed reporting, external validity, bias, confounding, and power [32]. This instrument is one of 12 appropriate for use in assessing observational studies [35]. Differences between reviewers were resolved by consensus.

Results

Literature Search Results

The search identified 2027 abstracts. After excluding duplicates (n=448), 1579 abstracts remained (900 from MEDLINE and 679 from PsychINFO). Review of the Cochrane databases produced no additional articles. Of the 1579 studies, 151 (10%) were excluded because they did not focus on adult subjects, 1259 (80%) because the subjects did not meet criteria for current depression, 113 (7%) because they did not assess alcohol problems or use, 21 (1%) because of the presence of polysubstance use, and one (<1%) because it did not address prevalence or outcomes. Four additional manuscripts [23, 36-38] were identified through review of bibliographies, resulting in the identification of 38 papers.

Among these 38 papers, two [39, 40] were excluded because more complete data were subsequently published [20, 41]. The one paper that addressed alcohol use [42] was excluded, leaving 35 papers. The diversity of research designs, heterogeneous definitions of alcohol problems, and diversity of outcomes precluded meta-analysis [43]. Of the 35 studies, 20 (57%) addressed the prevalence of alcohol problems in depression, six (17%) addressed their impact on depression, and nine (26%) addressed both.

Description of Studies

Twenty-eight (80%) studies defined depression using the Diagnostic and Statistical Manual [12, 44-46]. Others used the Research Diagnostic Criteria [47] (n=2,

6%), the Schedule of Affective Disorders and Schizophrenia [48, 49] and the Research Diagnostic Criteria [47] (n=1, 3%), the International Statistical Classification of Disease and Related Health Problems [50] (n=2, 6%), the Feighner criteria [11] (n=1, 3%), or clinician diagnosis (n=1; 3%). Twenty-four of 35 (68%) studies defined alcohol problems using Diagnostic and Statistical Manual criteria, with the remainder using the Research Diagnostic Criteria (n=2, 6%), the International Statistical Classification of Disease and Related Health Problems (n=2, 6%), the Feighner criteria (n=1, 3%), quantity/frequency measures (n=1, 3%), or no operational definition (n=5, 14%).

Recruitment strategies were described as hospital admissions/outpatient visits (n=16, 46%), sampling (n=7, 20%), study recruitment (n=5, 14%), and volunteers (n=5, 14%). Two studies (6%) did not specify recruitment procedures. Eighteen studies (51%) reported subject age with the mean age ranging from 32 to 63 years. Twenty-two studies (63%) reported sex with the majority of the subjects being women.

Prevalence Studies

How common are alcohol problems in patients with depression? (Table 3)

Of the 29 prevalence studies, 15 (52%) examined current alcohol problems in depression while 10 (34%) addressed lifetime alcohol problems, and four (4%) addressed both. The median prevalence from the 19 studies of current alcohol problems was 16% (range=5-67%). The median prevalence of the 14 studies of lifetime alcohol problems was 30% (range=10-60%).

Three studies, including two national surveys, addressed the question of whether alcohol problems are more common in patients with depression than in the general population. In a study of general medicine outpatients, Sherbourne [51] found higher

rates of current and lifetime alcohol abuse and/or dependence in patients with depression, 6% and 19% respectively, than in those with hypertension, diabetes, or heart disease, 3 to 4% and 14 to 16%. Grant [20] found higher rates of current and lifetime alcohol problems in the patients with depression, 21% and 40% respectively, compared to those without depression, 7% and 16%, and the general population, 7% and 18%. Similarly, Regier [19] found a prevalence of lifetime alcohol problems to be 16% in the patients with depression compared to 13% in the general population.

We conclude that both current and lifetime alcohol problems are common in patients with depression, and more common than in the general population.

Outcome Studies

Of the 15 studies of depression outcomes, 10 (67%) addressed current alcohol problems and five (33%) addressed lifetime alcohol problems in persons with depression. Three (20%) were randomized clinical trials, while twelve (80%) used an observational design. The studies categorized alcohol problems as at-risk drinking (n=1, 7%), and alcohol abuse and dependence (n=14, 93%).

Will the course of the patient's depression and response to antidepressant therapy be affected by alcohol problems? (Table 4)

Two of six studies examining the effects of alcohol problems on depression course reported an increased risk of relapse and decreased likelihood of recovery. Cook found that patients with lifetime alcohol problems and current depression had more hospital readmissions for depression (25% vs. 0%, p=0.004), a lower rate of recovery from depression one month after hospital discharge (25% vs. 55%, p=0.05), and were

more likely to describe a lack of overall improvement in depression at follow-up (43% vs. 12%, $p=0.014$) than patients with depression alone [27]. Similarly, Mueller found that lifetime alcohol problems decreased the likelihood of recovery from depression from 2.3% to 1.2% over 10 years [29]. In contrast, three studies found no association between alcohol problems and relapse or recurrent episodes of depression [26, 52, 53]. It is interesting to note that Leibenluft found that patients with depression and alcohol dependence reported increased alcohol use in response to depressive symptoms and increased likelihood of alcohol relieving these symptoms than those without alcohol dependence [54].

Overall, the studies examining the efficacy of antidepressants in depression and alcohol problems reported a decrease in depressive symptoms, despite the patients having concomitant alcohol problems. One open-label study of fluoxetine in patients with depression and alcohol dependence found statistically significant reductions on standardized depression scales such as the Hamilton Depression Scale (-6.4 , $p<0.01$) and the Beck Depression Inventory (-10.6 , $p<0.005$) [36]. The first of two subsequent placebo-controlled randomized clinical trials performed found a non-statistically significant improvement in depression scores in the treatment group [55]. The second larger study found a statistically significant inter-group difference between the fluoxetine group and the placebo group on the Hamilton Depression Scale (-6 ± 9.6 vs. -2 ± 13.3), $p=0.05$) but a non-statistically significant improvement on the Beck Depression Inventory (-6.5 ± 12.8 vs. 0.9 ± 12.1 , $p=0.17$) [56]. In a follow-up case series of 31 of these patients, the degree of depressive symptoms in the fluoxetine group changed minimally during the year following completion of the trial, providing evidence that the beneficial effects of fluoxetine persisted even in persons with alcohol dependence [57].

An unblinded study of patients with depression who were receiving antidepressant treatment compared the outcomes of those with and without a diagnosis of lifetime alcohol dependence and found similar rates of remission of depressive symptoms in both groups [56]. However, when the level of alcohol use was included in the analysis, subjects with greater alcohol use (≥ 28 drinks/week) had significantly smaller changes in their depression scores (-8.3 vs. -14.3, $p=0.007$) than those with lower levels of alcohol use (≤ 28 drinks/week) [56].

We conclude that the data on alcohol's effect on depression course are equivocal but that there is evidence that antidepressants can be effective in patients with alcohol problems.

Do alcohol problems affect the risk of suicide/death in patients with depression? (Table 5)

Four observational studies examined the risk of suicide/death as a depression outcome [27, 28, 58, 59]. While all four studies concluded that a current or lifetime alcohol problem in patients with depression was associated with an increased risk of severe suicidal symptoms or acts, only two studies had statistically significant results ($p<0.05$) [28, 58].

We conclude that alcohol problems may increase the risk of suicide/death in patients with depression.

What is the impact of alcohol problems on social functioning and healthcare utilization for patients with depression? (Table 6)

Hirschfeld found that depressed patients with a current alcohol problem had impaired relationships with their spouses at index, six months, and 12 months (all $p<0.01$) but not after 24 months [26]. Similarly, Cook examined the effect of alcohol

problems on interpersonal relations in persons with depression and found a higher rate of divorce (38% vs. 4%, $p=0.003$) and living alone (46% vs. 15%, $p=0.02$) [27]. Two studies examined the effect of alcohol problems on health care utilization for depression [27, 60]. In a study of 10036 depressed persons with and without alcohol dependence, those with current alcohol dependence had more hospital days (199 vs. 100, $p<0.002$) and outpatient visits (200 vs. 141, $p=0.002$) over four years [60]. In contrast, Cook observed fewer hospital days (22 \pm 12 vs. 49 \pm 53, $p=0.004$) over a four-year period in a study of 58 patients with lifetime alcohol problems and current depression [27]. In addition to notable differences in sample size, the former study examined current alcohol problems while the latter examined lifetime alcohol problems.

We conclude that alcohol problems have deleterious effects on social functioning and current, but not lifetime, alcohol problems increase healthcare utilization.

Alcohol Categories and Treatment Settings

In which alcohol categories and treatment settings have patients with depression and alcohol problems been evaluated?

The studies we identified examined a limited number of categories of alcohol problems including at-risk drinking ($n=1$, 3%), alcohol abuse ($n=4$, 11%), alcohol dependence ($n=9$, 26%), combined alcohol abuse/dependence ($n=17$, 49%), and alcoholism ($n=4$, 11%). Thirty-four of 35 (97%) of studies focused on the more severe forms of alcohol problems, namely alcoholism, alcohol abuse and alcohol dependence. With regard to treatment setting, 25 of 35 studies (71%) were conducted in psychiatric settings, 16 (46%) examined inpatients while 11 (31%) examined outpatients. Three

(9%) studies were based in primary care, four (11%) were in both psychiatric and primary care settings, and three (9%) did not specify.

We conclude that few studies have been conducted that evaluate low levels of alcohol use in primary care settings.

Quality of Evidence

Randomized clinical trials

Of the three randomized clinical trials, two (67%) were assigned a quality score of 3 out of a possible 5 points, indicating excellent quality, [55, 56] while one (33%) received a score of 1, indicating poor quality [57, 61]. None of the studies had an appropriate description of randomization or of the number of reasons for patient withdrawal. Two (67%) provided an appropriate description of double blinding [55, 56]. The two reviewers had 100% agreement in their ratings.

Observational studies

The mean quality score (of a maximum of 31) for the seven cohort studies was 16.1 (range=14-20), 10.5 (range=4-15) for the four cross-sectional studies, and 13.5 (range=12-15) for the two case series. The cohort studies also scored higher than the other types of studies on reporting, bias, and confounding. The evaluation of external validity was high for all but one of the studies [54]. None of the 12 observational studies addressed power. The two reviewers had 100% agreement in their ratings.

Discussion

Our review reveals that alcohol problems are prevalent in patients with depression, with median rates of 16% for current alcohol problems and 30% for lifetime alcohol problems. The studies that compared these rates with those of non-depressed patients or of the general population found higher rates of current and lifetime alcohol problems in depressed patients. The identified literature supports the efficacy of antidepressant therapy in patients with depression and alcohol problems. It also provides evidence of the association between alcohol problems and adverse depression outcomes. Specifically, alcohol problems in depression are associated with a worse depression course, an increased risk for relapse to and decreased likelihood of recovery from depression, increased suicide/death risk, worsening social functioning, and increased healthcare utilization.

Of note, the literature we reviewed focuses almost exclusively on alcohol abuse and dependence. Studies of lower levels of alcohol use such as at-risk, hazardous, or harmful drinking that primary care physicians are more likely to provide care for are rare. Further, most studies were conducted in psychiatric settings, limiting their relevance to primary care. Given that the majority of patients with depression or alcohol problems seek treatment in a primary care setting [60-63], it is important to determine whether similar results will be found in this setting and across the spectrum of alcohol problems.

Prevalence estimates for alcohol abuse and dependence in the general population range between 7% for current and 16 to 24% for lifetime alcohol problems [22, 62]. Our review of alcohol abuse and dependence in patients with depression revealed higher prevalence estimates than those found in the general population. Prevalence estimates for

less severe alcohol problems in large primary care- and population-based studies range between 0.3 to 29%. [14-18, 63] Unfortunately it is not possible to compare these prevalence estimates to those found in patients with depression as our review reveals that these surveys have not yet been reported.

There are limitations to this review. Relatively few studies examined alcohol problems in depression and the methodological quality of these studies was variable. The clinical trials often did not provide complete information about study design or information on subject follow-up. Many studies used a range of recruitment strategies, and had small sample sizes with short periods of observation, limiting their generalizability and the ability to assess the duration of effects. While 11 of the 12 observational studies achieved high scores on external validity, these studies performed less well in other areas. The studies used an array of diagnostic criteria and outcome measurements, making it challenging to arrive at comprehensive conclusions about prevalence and outcomes. The observational studies examining the effects of alcohol on depression outcomes presented equivocal findings. In contrast, antidepressant therapy was found to be effective in depressed patients with alcohol problems. A major caveat with these findings is that all but one of these studies were conducted by the same research group using sub-samples of the same patient cohort.

Despite the high rate of alcohol problems in persons with depression, we found a general dearth of treatment research in this area. One explanation is that these individuals are often excluded from randomized trials of antidepressants. In a recent randomized double-blind antidepressant trial, 17% of excluded patients had an alcohol or drug use disorder [64].

Our review concludes that alcohol problems are prevalent in patients with depression, they are associated with adverse clinical and healthcare utilization outcomes, and antidepressants can effectively treat depression in the setting of alcohol problems. These findings, however, are limited by the fact that these studies were primarily conducted in patients with the most extreme degrees of alcohol problems and in a narrow scope of clinical settings. In order to more broadly answer the clinical questions we posed, the prevalence and effects of varying levels of alcohol use among depressed patients treated in a variety of clinical settings must be examined. Providing clinicians with this information will enable them to accurately assess the impact of varying levels of alcohol use on their patients' depression treatment and overall quality of life and to offer better therapies to minimize this impact.

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Table 1. Specific Medical Subject Headings (MeSH) Terms, Main Terms, and Text Words in MEDLINE and PSYCHINFO Used to Identify Articles on Alcohol Use in Major Depression

MEDLINE Concept	MEDLINE MeSH Terms	MEDLINE Text Words
Alcohol	Alcoholism, alcohol drinking, ethanol, alcohol-related disorders, drinking behaviors	Alcohol, alcohol abuse, alcohol dependence, alcohol use disorders, problem drinking, hazardous drinking, heavy drinking, alcoholic, alcohol intake, alcohol consumption, harmful drinking, at-risk drinking
Depression	Depressive disorder, anti-depressive agents, depression	Major depression, unipolar depression, depressed patients, primary depression
Prevalence	Prevalence, comorbidity	

Outcomes	Treatment outcome, patient compliance, quality of life, morbidity, mortality	Treatment response, medication adherence, psychosocial functioning,
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PSYCHINFO Concept	PSYCHINFO Main Terms	PSYCHINFO Text Words
Alcohol	Alcoholism, drinking behaviors, alcohol drinking patterns, ethanol, alcohol abuse	Alcohol, alcohol abuse, alcohol dependence, alcohol use disorders, problem drinking, hazardous drinking, heavy drinking, alcoholic, alcohol intake, alcohol consumption, harmful drinking, at-risk drinking
Depression	Major depression, anti-depressant drugs	Depression (depress\$)
Prevalence	Comorbidity	Prevalen\$, comorbid\$

Outcomes

Treatment outcomes,
patient compliance,
quality of life

Morbidity, mortality treatment response, medication
adherence, psychosocial functioning

Table 2. Categories and Definitions for Alcohol Problems

Category	Definition	Organization or Classification System
At-risk drinking	Men > 14 drinks per week or > 4 drinks per occasion Women > 7 drinks per week or > 3 drinks per occasion	National Institute on Alcoholism and Alcohol Abuse (NIAAA)
Hazardous drinking	At risk for adverse consequences from alcohol	World Health Organization (WHO)
Harmful drinking	Alcohol is causing physical or psychological harm	World Health Organization (WHO)
Alcohol abuse	One or more of the following events in a year: Recurrent use resulting in failure to fulfill major role obligations Recurrent use in hazardous situations Recurrent alcohol-related legal problems (e.g. driving under the influence) Continued use despite social or interpersonal problems caused or exacerbated by alcohol	American Psychiatric Association (APA)
Alcohol dependence	Three or more of the following events in a year: Tolerance	American Psychiatric Association (APA)

Increased amounts to achieve effect

Diminished effect from same amount

Withdrawal

Substantial time spent obtaining, using, or recovering from alcohol's effects

Important activities given up or reduced because of alcohol

Drinking more or longer than intended

Persistent desire or unsuccessful efforts to cut down or control alcohol use

Use continued despite being aware of having a psychological problem caused or exacerbated by alcohol

Alcoholism

According to specific classification system

Schedule of Affective Disorders and
Schizophrenia (SADS)/ Research
Diagnostic Criteria (RDC)
Research Diagnostic Criteria (RDC)
International Statistical Classification
of Disease and Related Health
Problems (ICD) criteria
Feighner criteria

Table 3. Studies Reporting Prevalence Estimates

Source/ Year	Treatment Setting	Age (mean +/-SD, range, years)	Sex (% male)	Category of Alcohol Problem	Prevalence of Major Depression (n/N, %)	Prevalence of Alcohol Problems (n/N, %)	Prevalence of Alcohol Problems in Major Depression, (n/N, %)
Hirschfeld et al,[26] 1989	Multi-center NIMH study: psychiatric inpatient/ outpatient	Major Depression without alcohol: 42+/- 16; Major Depression with alcohol: 36+/- 13	42	Current abuse/dep endence	368/1,000=37%	79/368=21%	79/368=21%
Loo et	Multi-center	Not stated	Not	Current	816/1,231=66%	277/1,231=2	139/816=17%

al,[65]	study:		stated	abuse/dep		3%	
1990	psychiatric			endence			
	inpatient/outpati						
	ent						
	antidepressant						
	trial						
Sanderson	Psychiatric	36+/-12	44	Current	197/576=34%	Not stated	16/197=8%
et al,[37]	outpatient clinic			abuse/dep			
1990				endence			
Speer et	Mental health	63	36	Current	55/128=43%	29/128=25%	3/55 = 5%
al,[66]	institute			abuse/dep			
1992	residential			endence			
	program						
Sherbourne	Medical	Not stated	Not	Current	775/2,195=35%	Not stated	6%
et al,[51]	Outcomes Study:		stated	abuse/dep			

1993	community outpatient practice, hospital-based clinic, HMO, general medical providers/ mental health specialists			49	Current abuse/dep endence	109/109=100%	35/109=32%	35/109=32%
Mulder et al,[67]	Recruited patients,	Not stated		49	Current abuse/dep endence	109/109=100%	35/109=32%	35/109=32%
1994	unspecified setting							
D'Mello et al,[68]	Psychiatric inpatient hospital	Not stated	Not stated		Current abuse/dep endence	9/58=16%	36/58=62%	6/9=67%

1995					endence			
Grant et al, [20] 1995	Community household survey	Not stated	Not stated	33	Current abuse/dependence	1427/42,862=3%	7%	Abuse/dependence: 21%
					Lifetime abuse/dependence		Abuse/dependence: 18%	Abuse/dependence: 40%
Salloum et al,[69] 1995	Inpatient/outpatient at academic psychiatric facility	<40 40-60 60+	51% 29% 20%	33	Current abuse/dependence	2,660/8,139=33%	993/8,139=12%	239/2,660=9%
Fischer et al,[70] 1998	Psychiatric inpatient hospital	Median: 39	38		Current abuse/dependence	293/293=100%	Not stated	91/293 = 31%

Lin et al,[71] 1998	V.A. psychiatric inpatient hospital	Not stated	Not stated	Current abuse/dep endence	14/49=29%	6%	7%
Winokur et al,[72] 1998	NIMH Collaborative Depression Study	Not stated	Not stated	Current abuse/dep endence Lifetime abuse/dep endence	678/678=100%	15%	102/678=15%
Parikh et al,[73] 1999	Community survey	35	33	Current abuse/dep endence	333/8116=4%	Not stated	52/333=16%
Lyketsos et al,[74] 1999	Primary care/psychiatric outpatient	50-58	29	Current abuse	768/768=100%	Not stated	153/768=20%

	practices						
Fortney et al, [60] 1999	Primary care/psychiatric inpatient/outpatient V.A. hospital	Major Depression without alcohol: 52; Major Depression with alcohol: 44	96	Current dependence	10,036/67,878=15%	50,988/67,878=75%	6,034/10,036=60%
Kessing et al, [28] 1999	Psychiatric inpatient	Not stated	Not stated	Current abuse/dependence	17,477/20,350=86%	Not stated	Median=5% (range=2% for first hospital admission for major depression to 17% for 10 th hospital admission)
Bartels et al, [59]	Primary care outpatient	Not stated	Not stated	Current at-risk	689/2,240=31%	620/2,240=28%	52/689=8%

2002	hospital/V.A./community health center—Primary Care Research in Substance Abuse and Mental Health for the Elderly (PRISME) Study			drinking			
Melartin et al,[52] 2002	Psychiatric inpatient, primary care outpatient	40 +/-11	27	Current abuse/dependence	269/542=50%	Not stated	Abuse/dependence: 66/269=25% Inpatients: 39% Outpatients: 22% Abuse/dependence: 25%
Regier et	NIMH	Not stated	Not	Lifetime	6-month: 3%	14%	Abuse/dependence=17%

al,[19] 1990	Epidemiological Catchment Area (ECA) Survey of households, residents of long-term mental hospitals, nursing homes, penal institutions		stated	abuse/dep endence	1-month: 2%	(N=20,291)	
Brady et al,(54) 1991	Psychiatric inpatient hospital	Not stated	Not stated	Lifetime abuse	23/100=23%	68%	50-60%
Cook, et al,[27] 1991	Primary care V.A. inpatient	Major Depression without	100	Lifetime abuse/dep endence	58/58=100%	16/58=28%	16/58=28%

alcohol:

62+/-9 (55-

84) Major

Depression

with alcohol:

58+/-5 (55-

67)

Mueser et al,[75] 1992	Psychiatric inpatient	41	40	Lifetime abuse/dep endence	47/263=18%	Not stated	22/47=47%
Leibenluft et al,[54] 1993	NIMH outpatient research subjects or recruited locally	Not stated	Not stated	Lifetime abuse/dep endence	59/218=27%	40/218=18%	24/59=41%
Mueller et	NIMH	Major	40	Lifetime	588/955=62%	Not stated	176/588=30%

Abraham et al,[77] 1999	Psychiatric hospital outpatient	Not stated	Not stated	Lifetime dependence	375/375=100%	Not stated	37/375=10%	
Rae et al,[61] 2002	Outpatient psychiatric clinic	Non-alcohol dependent: 32	Non-alcohol dependent: 41	Lifetime dependence	180/180=100%	148/180=82%	<u>Overall Dependence:</u> 30%	
		Alcohol dependent: 32	Alcohol dependent: 48		Non-alcohol dependent: 126	Alcohol dependent: 54	<u>Drinks/week</u> <u>Non-dependent</u> <u>Dependent</u> <u>Total</u>	
							None	14%
							4%	18%
							≤ 3	27%
							8%	35%
							4-7	11%
							4%	15%
							8-14	12%

3% 15%

15-27 4%

3% 7%

>28 2%

8% 10%

Use in non-dependent

patients: $121/126=96\%$

Use in dependent patients:

$47/54=87\%$

Zimmerman et al, [38] 2002	Psychiatric outpatient practice	39+/-12	32	Current abuse/dependence	479/1,300=37%	Not stated	29/479=6%
				Lifetime abuse/dependence			181/479=38%

Table 4. Impact of Alcohol Problems on the Course of Depression and Response to Antidepressant Therapy (N=10)

Source/Year	Patients with Major Depression (N)	Treatment Setting	Category of Alcohol Problem	Study Design Jadad Score/Quality Index Score	Outcome in Presence of Alcohol Problems
Cook et al, [27]1991	58	Primary care V.A. inpatient	Lifetime alcoholism	Cohort Score=15	Decreased proportion receiving electroconvulsive therapy during hospital admission (13% vs. 43%, p=0.027) Increased proportion receiving tricyclic antidepressant medications alone during hospital admission 81% vs. 40%, p=0.005) Decreased full acute major depression treatment response (25% vs. 41%, p=reported as non-significant)

Mueller et	588	Psychiatric	Lifetime alcoholism Cohort	<p>Increased proportion receiving tricyclic antidepressant medications at time of hospital discharge (88% vs. 57%, p=0.027)</p> <p>Increased proportion with hospital re-admission (25% vs. 0%, p=0.004)</p> <p>Decreased proportion describing maximum recovery one month post-hospital discharge (25% vs. 55%, p=0.05)</p> <p>Increased proportion describing a lack of overall improvement in major depression at follow-up (43% vs. 12%, p=0.014)</p> <p>Decreased likelihood of recovery</p>
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al, [29]1994		inpatient/outpatient		Score=15	from major depression over 10 years (6/520=1.2% per week vs. 15/520=2.3% per week)*
Hirschfeld et al, [26]1989	368	Psychiatric inpatient/outpatient	Current alcoholism	Cohort Score=14	Level of alcohol use had no effect on mean time (in weeks) to recovery from major depression (Wilcoxon Chi-sq=0.14) or relapse to major depression Level of alcohol use/Mean weeks to recovery
					Mild-moderate 43
					Severe 53
					Very severe 38
Labbate et al, [53]1997	96	Primary Care inpatient	Lifetime abuse/dependence	Cohort Score=16	Patients with three or more previous hospital admissions for major

					depression were not significantly more likely to have an alcohol problem than patients who were being admitted to the hospital for the first time (11/46=24% vs. 6/50=12%, p=reported as non-significant)								
Melartin et al, [52]2002	269	Psychiatric inpatient/general medicine outpatient	Current abuse/dependence	Cross-sectional Score=15	No difference in number of major depressive episodes in patients with alcohol problems: <table border="1"> <thead> <tr> <th>Number of episodes</th> <th>Odds Ratio (95% CI)</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>1.0</td> </tr> <tr> <td>2</td> <td>0.8 (0.4-1.8)</td> </tr> <tr> <td>3</td> <td>1.3 (0.7-2.6)</td> </tr> </tbody> </table>	Number of episodes	Odds Ratio (95% CI)	1	1.0	2	0.8 (0.4-1.8)	3	1.3 (0.7-2.6)
Number of episodes	Odds Ratio (95% CI)												
1	1.0												
2	0.8 (0.4-1.8)												
3	1.3 (0.7-2.6)												
Leibenluft et	59	Psychiatric	Lifetime	Cross-sectional	Increased use of alcohol in response								

al, [54]1993		outpatients	dependence	Score=4	to depressive symptoms and increased likelihood that alcohol relieved depressive symptoms (specific level of increase not reported)
Cornelius et al, [36]1993	12	Psychiatric inpatient	Current dependence	Case series: 8-week open-label of fluoxetine Score=13	Improved score on Hamilton Depression Scale (change=-6.4, p<0.01); improved score on Beck Depression Inventory (change=-10.6, p<0.005)
Cornelius et al, [55]1995	21	Psychiatric inpatient	Current dependence	12-week double-blind, placebo-controlled randomized	Improved score on Hamilton Depression Scale (Fluoxetine group: change=-9.1+/-10.5 vs Placebo group: -1.9+/-16.6, p=NS) Improved score on Beck Depression

				clinical trial of fluoxetine Score=3	Inventory (Fluoxetine group: change=-7.6+/-11.2 vs. Placebo group: 0.56+/-14.9, p=0.18)
Cornelius et al, [56]1997	51	Psychiatric inpatient	Current dependence	12-week double-blind, placebo-controlled randomized clinical trial of fluoxetine Score=3	Improved score on Hamilton Depression Scale (Fluoxetine group: change=-6+/-9.6 vs Placebo group: -2+/-13.3, p<0.05) Improved score on Beck Depression Inventory (Fluoxetine group: change=-6.5+/-12.8 vs. Placebo group: 0.9+/-12.1, p=0.17)
Cornelius et al, [57]2000	31	Psychiatric inpatient	Current dependence	Case series of fluoxetine (1-year follow-up from Cornelius	Persistent efficacy of fluoxetine with continued improved Hamilton Depression Scale (Fluoxetine group score=13.1+/-8.9 vs Placebo group

et al, 1997 score=21.8+/- 11.9, p=0.016)
 study) And improved Beck Depression
 Score=13.5 Inventory (Fluoxetine group
 score=10.5+/-9 vs. Placebo group
 score=15.8+/- 10.7, p=0.042)

Rae et al, [61]2002	180	Psychiatric outpatient	Lifetime dependence	6-week randomized clinical trial of fluoxetine/ nortriptyline	Improved score on Hamilton Depression Scale in three alcohol groups: Level of Alcohol Use Change in score 1) Non-dependent -12.3 2) Dependent, ≤28 drinks/week:- 14.3 3) Dependent, >28 drinks/week: -8.3 (3 vs. 2: p=0.007, 3 vs. 1: p=0.027)
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*No indicator of significance reported

Table 5. Impact of Alcohol Problems on the Risk of Suicide/Death (N=4)

Source/Year	Patients with Major Depression (N)	Treatment Setting	Category of Alcohol Problem	Study Design Jadad Score/Quality Index Score	Outcomes in Presence of Alcohol Problems
Cornelius et al, [58]1995	5,732	Psychiatric outpatient	Current dependence	Cross-sectional Score=12	Increased suicidal symptoms (scored as 0=symptom not present, 1=mild, 2=moderate, 3=severe; depressed alcoholics had mean score=1.6+/-1.2 vs. depressed non-alcoholics had mean score=1+/-0.97, p<0.001)
Kessing et al, [28]1999	20,868	Psychiatric inpatient	Current alcoholism	Cohort Score=15	Increased risk of suicidal act (hazard ratio (95% CI)=1.4 (1.2-1.7), p<0.001)or suicide (hazard ratio (95% CI)=1.8 (1.1-3.1), p<0.05)
Bartels et al, [59]2002	689	Primary care outpatient	Current at-risk drinking	Cross-sectional Score=11	Increased suicidal ideation in presence of alcohol (15% vs. 12%) and decreased death ideation (27% vs. 34%)*

Cook et al, [27]1991	58	Primary care inpatient	Lifetime alcoholism	Cohort Score=15	Increased all-cause mortality 25% vs. 12%*
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*No indicator of significance reported

Table 6. Impact of Alcohol Problems on Social Functioning and Healthcare Utilization for Major Depression (N=3)

Source/Year	Patients with Major Depression (N)	Treatment Setting	Category of Alcohol Problem	Study Design Jadad Score/Quality Index Score	Outcome in Presence of Alcohol Problems
Hirschfeld et al, [26]1989	368	Psychiatric inpatient/outpatient	Current alcoholism	Cohort Score=14	Impairment in spousal relationship assessed using the Longitudinal Interval Follow-up Evaluation (LIFE) scale with significant differences at index, 6 months, and 12 months (all $p<0.01$), but not at 18 or 24 months. Impaired social functioning at index (NS), 6 months, 12 months, 18 months, and 24 months (all $p<0.05$)
Cook et al, [27]1991	58	Primary care inpatient	Lifetime alcoholism	Cohort Score=15	Higher rate of divorce at follow-up (38% vs. 4%, $p=0.003$) and living alone (46% vs. 15%, $p=0.02$), Decreased hospital days (49+/-53 vs.

					22+/- 12, p=0.004)
Fortney et al, 10,036 [60]1999	Psychiatric and primary care inpatient/outpatient	Current dependence	Cohort Score=18		Increased hospital days (199 vs. 100, p<0.002), increased outpatient visits (200 vs. 141, p=0.002) (used retransformed expected values of adjusted log means)