"PREVALENCE AND CORRELATES OF MAJOR DEPRESSION AND ANXIETY DISORDERS AMONG PATIENTS WITH ALCOHOL-USE DISORDERS IN NEPAL"

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THESIS SUMMARY

Submitted as a part of the Master of Philosophy Degree in International Community Health

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To Dipak and Olav

Fig 1.(1)

Coveted Pleasure
Frothy scintillas of oblivion
Candleflies' cascade

- Sudan Prasad Neupane, 2011

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UiO : 200

UiO : Institute of Health and Society
University of Oslo

UiO : Faculty of Medicine
University of Oslo

Norwegian Centre for Addiction Research

The PROJECT

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PREFACE

Presentation plan:

This thesis is being submitted as part of Master of Philosophy degree in International Community Health at the University of Oslo. The current submission follows option 2 among the forms of thesis accepted as highlighted in the circular *Requirements of the MPhil Thesis,* February 2011 from the Department of Community Medicine. Hence, results and discussion of findings is not included.

As presented in the materials section, voluminous data were collected. The thesis is started with an abstract of the first paper submitted for publication. This follows the literature review section in which a relevant description of the study theme, focused but not limited to the variables, used in the first paper is presented.

Brief methodological consideration is presented together with detailed methods and materials in the Methodology section. List of cited references, pertinent appendices and a copy of the submitted paper concludes this write-up.

ABBREVIATIONS

ALP:	Alkaline Phosphatase
APA:	American Psychiatric Association
AUD:	Alcohol-use disorders
CBS:	Central Bureau of Statistics (Nepal)
CDT:	Carbohydrate Deficient Transferrin
CIDI:	Composite International Diagnostic Interview
DALYs:	Disability Adjusted Life Years
DSM-IV:	Diagnostic and Statistical Manual of Mental Disorders version IV
EtG:	Ethyl Glucuronide
FDA:	Federal Drug Administration of the United States
GAD:	Generalized Anxiety Disorder
GGT:	Gamma Glutamyl Transferase
HSCL-25:	Hopkins Symptom Check List-25
ICD-10	International Statistical classification of Disease and Related Health Problems (10th Revision)
ISBRA:	International Society for Biomedical research on Alcoholism
MD:	Major Depression
NESARC:	National Epidemiologic Survey on Alcohol and Related Conditions
SCID:	Semi structured Clinical Interview
SSB:	Statistics Central Bureau (Norway)
SERAF:	Norwegian Centre for Addiction Research
TUTH:	Tribhuwan University Teaching Hospital
WHO:	World Health Organization
WHO-AIMS:	World Health Organization- Assessment Instrument for Mental Health Systems

Abstract[1]

Comorbidity of major depression in alcohol-use disorders: the case of Nepal

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Introduction Nepal is an ambivalent society in terms of alcohol use: alcohol consumption is frowned upon among traditionally ruling upper caste people whereas its use is socially accepted among certain lower caste people. We hypothesized that presence of social taboo leads to higher rates of depression among consumers of alcohol and that the explanations of comorbid depression across the two strata could be different. **Aims** 1) To investigate if belonging to the tabooed social stratum led to higher rates of concomitant major depression. 2) To correlate sociodemographic and clinical factors with the presence of major depression in the two social strata. **Methods** A cross-sectional survey was carried out among consecutively admitted 188 Alcohol-use disorder (AUD) patients in multiple residential alcohol treatment units in Kathmandu during the period July- December, 2010. We recorded socio-demographic data and administered the alcohol use and depression modules of WHO Composite International Diagnostic Interview (CIDI) 2.1, and the Alcohol-use disorder Identification Test (AUDIT). **Results** Depressed AUD patients compared to non-depressed AUD patients had significantly more severe alcohol problems and were less likely to be cohabitating with a partner. Lifetime and 12-month prevalence of major depressive episodes among the alcohol abuser/dependent patients were found to be 45% and 36% respectively, with marginally higher rates of major depression in the non-tabooed group. Lacking a stable employment, having experienced alcohol-induced blackout, and longer abstention were positively associated with major depression in the non-tabooed group. In case of the tabooed group, parental problem drinking appeared to be the single most important independent correlate (OR=7.7, 95% CI= 2.6-22.3) of comorbid MD. **Conclusions** Major depression is common among patients with alcohol-use disorders in Nepal. Among treatment seekers, social taboo on alcohol use seems to have insignificant effect on rates of comorbidity. However, lack of stable source of income and alcohol problem severity in case of the non-tabooed class and familial predisposition in case of the tabooed class may indicate potential risk factors for depressive comorbidity.

Keywords: Nepal, alcohol, depression, comorbidity, taboo.

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CHAPTER 1. INTRODUCTION

1.1 Background

The distribution of psychiatric illnesses including those related to alcohol use is universal and the burden is heavy. A mixed occurrence of two or more of these illnesses heralds challenges to reaching early diagnosis and institution of appropriate treatment- even among those who seek help. Failure to curb the problems rigorously and early in course of the disease increases risks of adverse outcomes in terms of physical, mental and social wellbeing as so happens in familial and professional fronts. Today, almost three quarters of the global burden of neuropsychiatric disorders occur in low- and middle-income countries (2;3). The dimensions of disease epidemiology may vary by regions. This is especially true in case of psychiatric morbidities where socio-cultural attribution may modulate relationships between the disorders.

Psychiatric comorbidity is a co-occurrence of more than one psychiatric diagnosis in the same individual at the same time, sometimes owing to diagnostic misclassification of underlying single pathology. Alcohol abuse and alcohol dependence, together called alcohol-use disorders (AUD), are often associated with comorbid conditions, nicotine dependence being the most common (4). This is followed by mood and anxiety disorders which are also quite often comorbid with alcohol-use disorders (5). Major depression is a cluster of symptoms of low mood and anhedonia as defined by American Psychiatric Association (see appendix). The co-occurrence of major depression in alcohol-use disorders is rather a rule than just chance (6;7).

Nepal is a low income secular republic lying between India and China and covers an area of 147,181 sq. km (8;9). The majority (80%) of its 29.3 million inhabitants follow Hinduism (9), a religion cum-culture, with its multifaceted construct of caste system. The caste determines an individual's behavior, obligations and expectations in the society (10), also those relating to the use of alcoholic beverages. The caste division, based on Hindu culture, and classified according to the profession, was formally authenticated by an archaic civil code *Muluki Ain* in 1854. The code also categorized the whole Nepalese society into two distinct groups according to the acceptability of alcohol consumption. One end of the caste system is the historically ruling upper class constituted by *Brahmins* (the priests and the

teachers) and *Kshatriyas (*the warriors and the rulers*)* who are considered 'purer' being twice born, wear holy thread on their body and among whom alcohol use is frowned upon. These people together constitute the *Tagadhari* community. On the other hand, the so called lower castes which include (traders, farmers, artisans, and labourers), identified by surnames *Rai, Limbu, Gurung, Magar, Tamang*, *Newars,* etc. constitute the *Matwalis.* Matwali literally means an alcohol user. Alcohol enjoys social and religious sanction among people belonging to this group. Although much of this observance has probably diminished (11), studies indicate that association of alcohol with taboo in certain caste and ethnicity is even valid today. For example, one study identified that the abstinence rates was 85% among the Tagadharis and 40% among the Matwalis (12). Thus Nepal is clearly an ambivalent society in regard to use of alcohol.

''A resource limited district hospital in Eastern hills of Nepal. In front of the outpatient clinic is a local bar, a glass of rice brewed (approx 20% ethanol) *Rakshi* costs 10 US cents equivalent Rupees. A laborer woman of middle ranked caste in her 40s is a regular customer. She is also the hospital client once in around 3 months-alcohol induced hepatitis/grade two hepatic encepahlopathy with known depressive disorder. Hospital admission deferred because of inability to pay. The husband (working as a security guard in Dubai) visits the clinician and asks if the sick liver could be replaced- the answer was yes, in UK. The woman dies in two months. The husband self-medicates the bereavement with *Rakshi;* meets the clinician in the town and shares his trouble- but denies psychiatric problems/treatment. Six months later the son is rushed to the hospital: diagnosis- acute stress reaction (the cause: the father had committed suicide). One day, the clinician finds the son injecting illicit drugs in a nearby temple; obviously drinks too.'' This vignette of vicious cycle may be representative of many untold stories of today's Nepal. The same makes the conceptual framework of this research work.

Home brewing and consumption of alcoholic beverages is common in most regions of the country. Despite strong social stigma associated against alcoholism, a growing wary of its increased use exists. Liquor production at home is one of the common employment ventures undertaken by women and the current liquor control act of Nepal allows the production of home-made forms of alcohol for domestic use (8). Home brewing is common in the rural settings, but also occurs in urban areas. A blending of oriental drinking culture survived by the practice of home brewing, and consumption of industrially brewed alcoholic drinks co-

exists in Nepal. There are no nationally representative population level data on the prevalence of alcohol-use disorders and other psychiatric diseases in Nepal. By and large, the scale of these problems is unknown. As a tip of an iceberg, a community survey in Eastern Nepal showed that as many as one in four adults living in Nepalese towns may be dependent to alcohol (13). Alcohol is thus considered a common commodity, but its morbidity may be an unscaled hillock of this mountainous country.

A complex socio-cultural dimension and poor health economics together make Nepal a unique ground for alcohol and related psychiatric morbidities. There is only one 'mental hospital' with a total of 0.20 beds per 100,000 populations (14). According to the same World Health Organization (WHO) report, a majority of these users are treated in outpatient facilities, mostly by non specialists. The total number of human resources working in mental health facilities or private practice per 100,000 population is 0.59 of which 0.13 are psychiatrists, 0.06 other medical doctors, 0.27 nurses, 0.02 psychologists, and 0.10 other health or mental health workers (14). These figures are comparable with the statistics from India (15) but in short of huge necessity as compared to the developed nations. For example, in Norway roughly 120 beds and 20 psychiatrists are available for every 100,000 population (16). The government of Nepal spends 0.08% of the total health budget on mental health while the family of the mentally ill has to spend out of pocket around 25,000 Nepalese Rupees (approximately USD 350) per year as direct services costs (14).

Given the resource constraints and stigma associated not only with alcoholism but also with other mental illnesses, it can be assumed that those patients who attend hospital represent a fraction of a much neglected problem. Excessive consumption of alcoholic drinks, being afflicted with mood disturbances, and having suicidal ideation are common vignettes of psychiatric presentations. Of particular concern in Nepal is an alarmingly high proportion of younger population whose drinking career starts even before adolescence (12). Few hospitals run detoxification services to substance dependent individuals and an increasing number of 12-step based rehabilitation centres are operating in urban areas. Too little is known about the patient characteristics and affective comorbidity among treatment receivers at these centres. Enduring social taboo on alcohol use germane to most oriental societies may have bearing in the depressive psychopathology. Conversely, such taboo may alter the threshold of self medicating behavior. There is a need to sensitize health professionals and draw administrative attention to raise efforts in effective identification and appropriate treatment of

those individuals. Moreover, there is an urgent need to carry out epidemiological studies to scale the seriousness of the problem. Biomedical researches with a potential of bridging gap of information from and between the rich and the poor nations are equally important to understanding the dimensions of epidemiology of psychiatric illnesses. Treatment units may provide important venues and insights to understanding the epidemiology of alcohol-use disorders comorbid with depression and/or anxiety disorders.

1.2 LITERATURE REVIEW

1.2.1 Burden of Alcohol-use disorders is heavy

Alcohol is probably the only legal and the commonest substance of abuse after nicotine in most regions of the world. Alcohol use started with prehistoric ages and has taken place throughout the past millennia; however, health outcomes of its use became a subject of concern only since last few decades. World Health Organization (WHO) estimates that there are about 2 billion people worldwide who consume alcoholic beverages and 76.3 million have a diagnosable alcohol-use disorder (16). The same report estimates 1.8 million annual deaths (3.2% of total) and 58.3 million (4% of total) of disability adjusted life years (DALYs) attributed to alcohol globally. Alcohol constitutes the largest risk factor for DALYs lost in middle income countries and the third largest in all income group countries (17).

Against the global average of 5.1 L, France, Ireland, Uganda, Luxemburg and Czech Republic (>13 L) top the list of adult per capita consumption of alcohol (2;16). WHO reports recent and steady increase in its consumption in the South East Asian region. The consumption of recorded alcohol in most Muslim populations and in South Asian countries seems to be lower than in Europe and Americas. However, unrecorded alcohol consumption is estimated to be at least two thirds of all alcohol consumption in the Indian subcontinent, about half of consumption in Africa, and about one third in Eastern Europe and Latin America (18). While drinking cultures keep the tradition alive, poverty and the majority of production via home brewing give vigor and social sanction to some groups provide a unique dimension to its use in Nepal. While the use of alcohol seems to be higher among the lower social strata people in the developed countries, its use may be a matter of exuberance among the higher strata in low income countries. However, the distribution of alcohol-use disorders is arguably rather universal.

The 12 months prevalence of alcohol dependence in US general population reported by a large survey (N=43,093) assessed by using DSM criteria was 8.5% (19). A community survey (n=2344) conducted in an Eastern town of Nepal using the CAGE questionnaire showed prevalence of alcohol dependence among 19.3% of the randomly selected general population (13). The latter study highlights middle aged illiterate males of lower caste as the most vulnerable group for alcohol dependence. A communication from WHO's World Health Survey (n= 8663) implicate Nepalese male youths to indulge in significantly higher (1.3%)

events of episodic drinking as compared to their female (0.3%) counterparts (20). The same survey, on the other hand, notes that females indulge in heavy and hazardous drinking more often (4%) than do males (3%). As high as 75% females and 53% males were life time abstainers in Nepal (21). But rates of past 12-month abstinence may be up to 45% higher (85% vs. 40%) among people who belong to the socially sanctioned group as compared to the group that has taboo on the consumption of alcohol (12).

A survey done among children and youths aged between 10 and 17 years (n = 426) in 16 districts of Nepal found that 17.4% of the respondents had consumed alcohol at least once in the preceding 12 month period (12). The prevalence among boys (21.8%) was almost double that of girls (11.2%) indicating gender variation in alcohol using population. The study also found that the rate of reported drinking in the past 30 days was 10.1% (boys) and 7.9% (girls). One half of those Nepalese children who were drinking initiated alcohol before the age of 13 (12). Unfortunately, nationally representative population level prevalence rates of alcohol consumption and related disorders are not available. Available data, however, illustrate that the problems related to alcohol is already an emergent public health issue in Nepal (12;13;22).

Studies have revealed that alcohol consumption is associated with more than 60 types of disease and injury (23). There is also evidence that about 20% patients seen in clinical practice may present underlying alcohol misuse, at least in the western settings (24;25); in Nepal as many as 16.5% physically ill persons referred to psychiatric consultation had an alcohol-use disorder (26). The contribution of patients attending hospital for treatment in Nepal, however, does not directly reflect such huge burden of alcohol related disorders. The extent of treatment seeking for one's alcohol related problems is unknown in the context of Nepal, but even in American NESARC study of general population, only 6% AUD patients sought treatment in the year preceding assessment (19). Even less is known as to who among them actually seek help. Among the indirect evidences of the burden of alcohol-use disorders may be the increasingly large number of alcohol and drug rehabilitation centres being operated in urban concentrations of the country.

1.2.2 Depression and anxiety disorders are common

WHO's 2005 report attributed 31·7% of all years lived-with-disability to neuropsychiatric conditions: the leading disorder that contributed to this total was Unipolar major depression

(11·8%) followed by alcohol-use disorders (3·3%) (27). In the American general population, the lifetime prevalence of generalized anxiety disorder (GAD) is 5.1%, with a 12-month prevalence measured at 3.1% with female preponderance (28), the median age of onset occurring during the early 20s (29). Depression is the leading cause of disability in the United States for individuals aged between 15 and 44 (16). Results from the American National Epidemiologic Survey on Alcoholism and Related conditions (NESARC) showed that the prevalence of 12-month and lifetime DSM-IV major depressive disorder was 5.3% and 13.2%, respectively. People from minority background (which includes Asians) are suggested to have a lower risk for MDD (30).

In the South African Stress and Health Study (n=4351), the 12-month prevalence of any DSM-IV disorder was found to be 16.5%, with 26.2% of respondents with disorder classified as severe cases and an additional 31.1% as moderately severe cases. The most common disorders were agoraphobia (4.8 %), major depressive disorder (4.9%) and alcohol abuse or dependence (4.5%) (31). Similar study from Israel showed 17%of the adult population had a lifetime occurrence of a mood or anxiety disorder, while nearly one in 10 (9.7%) reported a mood or anxiety disorder occurring during the previous 12 months (32). Mood disorders were twice as common as anxiety disorders (32).

Various studies from Nepal indicate higher rates of anxiety and depressive symptoms among vulnerable group of people. A cross-sectional survey conducted among 290 internally displaced persons in Nepal in 2003 showed alarmingly high rates of anxiety and depression symptomatology (80.7 and 80.3% respectively) while 53.4% had PTSD symptomatology (33). Approximately one in five tortured and nontortured Bhutanese refugees living in Nepal were found to be living with psychiatric disability (34). The prevalence in general population of an area in West Nepal was anxiety: 28%, depression: 30%, and a self reported distress of the so called *Jhum-Jhum*: 42% (35). Scale measures of anxiety and depression using Beck inventories classified a third of Nepalese adults in a hilly district as being depressed and a quarter being anxious (22). This raises a question of validity of measures of mental health across cultures. It is unfortunate that the tools for assessment of mental health standardized according to the ethnic dimensions and local context are hard to produce and available tools are less valid. Among psychiatric comorbidity in patients referred to psychiatrist from other disciplines, dissociative/conversion disorders were the commonest (17.2%) followed by alcohol use-related disorders (16.5%) and depressive disorder (13.2%) (26). There is a need

to characterize the burden of these psychiatric comorbidities in Nepalese clinics and a detailed investigation on their epidemiology is pending.

1.2.3 Association between alcohol-use disorder and depression/anxiety

Physical complaints are commonly encountered among alcohol consumers, both in community and clinical samples (36). Many other studies delineate alcohol-use disorders with other mental illnesses. Mood disturbances are arguably the most common psychiatric complaint among treatment seeking patients with an alcohol-use disorder, affecting over 80 percent of alcoholic abuser/dependent population at some point in their drinking careers (37;38). According to a review of epidemiological surveys, field studies and family studies, between 8.3% and 56.2% of inpatient alcoholics, with a median prevalence of 22.9% met the criteria for GAD (39). Joshua & Sarah (2010) came up with 46.2% of comorbidity between the two conditions strongly supporting the previous finding. The American National Epidemiologic Survey on Alcohol and Related Conditions further confirmed a positive and significant ($P<.05$) association between most substance use disorders and independent mood and anxiety disorders (19).

Consistently high rates of comorbidity have been found between alcohol-use disorders and a number of mood and anxiety disorders in both national epidemiological surveys (6;19;28;40) and clinical studies (41-43). The comorbidity seems to be more often met with alcohol dependence than alcohol abuse (44). While numerous studies (40;45) implicate major depression as a secondary pathology, many other studies (46;47), however, attribute alcohol abuse as a secondary illness – as a result of self medication for depressed mood. Independent substance abuse and mood disorders or anxiety states may also be common (48).

In a tertiary care hospital in Nepal approximately 83% of Psychiatric emergencies received the diagnosis of Category F of the ICD-10. Mental and behavioral disorder due to substance use (F10-19) was the most common disorder (30%), followed by mood/affective disorders (23%) and neurotic, stress-related anxiety disorders (16%) (49). Uncertainties exist about the prevalence and co-morbidity of alcohol-use disorders and independent mood and anxiety disorders. Depressive syndromes can both precede and follow the onset of alcohol dependence (50).

Alcohol-use disorders and major depression may be linked through several possible mechanisms: a) both are separate entities but are diagnostic orphans b) one disorder leads to another, and c) a common etiology exists leading to both the disorders.
Although many research works have tried to delineate the causal links between alcohol dependence and mood and anxiety disorders, little is consensual regarding the 'primariness'of either disorder. A recent review, and based mainly on the author's earlier analysis propose that causal links exist between the two disorders, with alcohol-use disorders being the more plausible primary phenomenon (51;52). This observation was supported by a Danish register-based study which, without rejecting the reverse temporal order, concluded that AUDs are usually the index pathologies (53). Despite the frequent comorbidity, no single definitive causal or common etiological predictors have been identified that underlies both the disorders (30). AUDs may be even more frequently comorbid with nicotine and other substance use disorders (54). Structural equation modeling used in such analyses, are however, far from comprehensible raising methodological issues.

An observational study conducted in a tertiary level hospital in Nepal showed that 50 out of 53 patients admitted with an ICD-10 diagnosis of mental and behavioral disorder due to the use of alcohol were suffering from depressive episode (55). This universality of the co-occurrence may be an exaggeration of symptom overlap; but it can be a reflection that severe mood disturbance may be a force driving help seeking behaviour.

1.2.4 Correlates of AUD-MD comorbidity

An analysis of acamprosate trial studies from 10 European countries showed that profiles of depressed patients among those with an alcohol-use disorder may be distinct from those who are not depressed (56). It identified five predictors of depressed patients as being female, younger, unemployed, living alone, and episodic drinker. However, it was not identified whether unemployment and divorce led to MD or Vice versa because the direction of these characteristics may go both ways. A large clinical inpatient dataset from Australia, however, suggested that male patients with mental disorder were more likely to have an AUD, but psychiatric comorbidity in general was more common among males (12% vs 7%); with younger age (20-49 years) than gender being more important predictor of comorbidity (57). A meta-analysis of studies from at least 64 clinical venues showed that age was a moderator of AUD- MD comorbidity where the association was stronger in older samples (30). Most of the studies in the meta-analysis indicated that early onset of habitual drinking was a predictor of

MD. The association with concurrent use of alcohol and other substance was also found to be consistent among the comorbid patients (30).

In gist, older age (30), early onset of alcohol abuse (58;59), white race (30;60), and low socioeconomic status (61) are often implicated as risk factors for major depression among patients with AUDs. Another notion attributes depressive comorbidity to the pattern of alcohol consumption and severity of problems caused by harmful drinking. Following Cloninger's proposed typologies of alcoholism (62), a number of studies have investigated the children of problem drinkers suggesting that parental problem drinking relates both to AUDs and depressive mood in the off-springs (63-65). The applicability of these findings needs to be corroborated in more regional settings. AUD patients belonging to racial/ethnic minority origin have been found to generally report lower levels of depression than do their Caucasian counterparts in Western settings (30). The argument that minority groups, probably with immigrant background are less likely to have unstable mood is contestable, and less convincing. Most of the literature by virtue of their research settings list Asian population as a minority group, or often as 'others' thus leading to no inferable details about them.

Earlier study from Nepal also showed a preponderance of co-occurring major depression among married males and educated clients from the towns over unmarried, females, and illiterate rural dwellers. People from the so-called upper castes had higher proportions of co-occurring depression disorders (55). This under-sampled clinical study was contested by Kohrt and colleagues (2009) by their multiple ethnographic and epidemiological approaches where they found lower socioeconomic status of people in the lower social strata (also on the basis of caste system) compared to dominant upper castes were much more (about double) prone to have depression and anxiety disorder (22). Yet another study of treatment seeking problem drinkers showed that about 42% of the alcohol dependent clients had concurrent major depression, which after detoxification fell to about 17% (66). A comprehensive understanding of the correlates of the co-occurrence of these two disorders is pending.

We have sufficient evidence to propose that caste based disparities in mental health in the context of Nepal is not just an artifact. Differential occurrences of comorbidity in the

background of socio-cultural tolerability of alcohol in an ambivalent oriental society are, however virgin lands of psychiatric research.

1.2.5 Comorbidity complicates either disorder and increases risk of self harm

It is can be argued that regardless of whichever disorder comes earlier in the sequential ordering of the comorbidity, the importance lies with identifying the predictors of the dual diagnosis and identification of effective interventions.

A prospective study from Iceland demonstrated that patients with no comorbid diagnoses had the fewest lifetime admissions; whereas agoraphobia/panic disorder predicted frequent readmission (odds ratio 5.8) (67). There is ongoing debate regarding the initiation of antidepressants among depressed patients with comorbid alcohol-use disorder (68). Co-occurring depression among AUD patients not only impairs neuropsychological functioning (69) but also predicts relapse to alcohol use (70) and increased risk for suicidal behaviour (71). Clearly, the clinical management of comorbid illness is complex and outcome less favorable. Integrated psychosocial, cognitive behavior therapy and pharmacotherapy form the basis of treatment among these individuals in developed setups. Quite ironically in populous third world countries, there are sufferers, and there are caregivers: but who are suffering, what they are suffering from, who treat them and how they are treated have so far remained meager issues.

There is no organized treatment in Nepal for what in the west is called a dual diagnosis. Baseline data on the same are needed to draw attention from clinical practitioners and policymakers.

Unintentional injuries alone account for about one third of the 1.8 million deaths attributed to alcohol annually, likewise neuropsychiatric conditions account for close to 40% of the 58.3 million DALYs (27). In general, affective disorders and substance use disorders are the most common diagnoses in suicides (72). Retrospective analyses have found between 25 % and 64% (73;74) of individuals committing suicide suffered from mood disorders; the contribution of bipolar disorders was just under 5% (72). Cheng and colleagues (1995) reported from Taiwan an overwhelming association (87%) between individuals committing suicides and having concomitant depressive disorder (75).

According to a cohort study of 4022 depressed Canadian patients, the standardized mortality ratio for suicide as a cause of death was 26-fold (76) and in a study of 40,000 Norwegian military conscripts who abusing alcohol were 6.9 times as likely to commit suicide as those who were not (77). Of the 1863 patients with a history of alcohol dependence or abuse and depressive symptoms included in a recent WHO/ International Society for Biomedical research on Alcoholism (ISBRA) study, over 15% had history of both the conditions; the subgroup analysis on comorbid AUD and depressive disorder showed strong correlation with suicidal ideation (78).

Depression, alcohol abuse and suicidality (suicidal ideation, plan and attempts) remain the great challenges of present global public health. The comorbidity of problem drinking, depression and suicidality among adolescents have been found to be very high (79). In a study from Singapore, 27% of completed suicides were attributable to depression but prevalence of substance abuse and comorbidity was found to be lower in Singaporean suicide subjects, which was a notable difference from other studies done in the Western countries (80). This probably reflects the regional differences in terms of comorbidity.

Suicide is the leading (16% of all) cause of death among women of reproductive age group in Nepal (81). Data are lacking regarding the pathway of suicidal ideation, substance use, familial predisposition, among other risk factors, to completed suicides. This makes suicide an integral component of the current study.

1.2.6 Classification system and assessment tools may explain some of the variations in psychiatric research findings.

Unlike most other medical conditions, diagnosis of many psychiatric disorders is not straight forward. Often the socio-cultural values, norms and clinician's judgment influence the diagnosis. Many symptoms of alcohol withdrawal and intoxication may overlap with those of mood and anxiety disorders thus complicating the diagnosis being made. Hence, a paucity of techniques that measure appropriately the index disorders and help to differentiate acute alcohol use related symptoms from axis I psychiatric disorders present a diagnostic challenge (19). Besides, classification system should be improved to facilitate quality improvement of mental health systems (82). Diagnostic misclassification weakens the brevity of psychiatric clinical practice and demands more research. However, the usefulness of even 'gold-standard' instruments has been challenged by cultural and ethnic dimensions of mental health (83).

Furthermore, studies conducted on the same theme may employ differing measures of disorders. A typical example is depression, which is elucidated in terms of major depression disorders, depressive episodes, depressive symptoms, psychological distress, among other measures. This hinders a generalisable understanding of the common phenomenon, making interpretations difficult. Many of the differences observed in studies discussed above may owe to the measures used. The social construct of mental disorders make the effort of uniformity of diagnosis even more challenging (84;85). Methodological issues pertaining to such research has been discussed in the section *methodological consideration*.

1.2.7 Objective measures of alcohol use and role of AUD in immune-modulation

Several biochemical and hematological parameters, such as gamma-glutamyltransferase (GGT) activity, aspartate aminotransferase (AST) activity, high density lipoprotein cholesterol (HDL-C) content of serum, and erythrocyte mean corpuscular volume (MCV) are established markers of alcohol intake (86). These investigations provide important prognostic information and can be used to monitor abstinence (86); at the same time these may provide complementary evidences for psychometric tests such as TLFB and AUDIT (87). These markers may be useful in substantiating the findings of structured questionnaire such as alcohol module of CIDI and AUDIT, and TLFB used in our study. The combination of those tests may give more accurate reflection of recent to several weeks of alcohol intake, and help to substantiate our findings of psychological distress and enduring depression disease. GGT is a useful and relatively more specific tool (compared to ALP and other biliary enzymes) to identify alcohol consumption over weeks. Carbohydrate deficient transferrin (CDT) is considered a better measure of heavy alcohol use and may serve as a prognostic indicator towards abstinence (88). A combination of CDT measure with GGT gives higer sensitivity and specificity towards alcohol intake (89). Ethyl glucuronide (EtG) is a direct metabolite of ethanol that can be detected in body fluids for a relatively longer period after complete clearance of ethanol from the body (87). Serum and urine levels of EtG can be useful in determining the time of recent ethanol intake making it a useful tool to monitor abstinence (90). EtG can also be detected in body fluids, and even hair at very low levels, making it an important measure of alcohol intake (91).

Alcohol is a known modulator of immune system and depression is suggested to cause alteration in cytokine profile consequently increasing susceptibility to infection. Independent

effects of major depression and alcohol dependence among alcohol-dependent persons on immune cell function have been investigated in experimental models (92). The role of AUDs as modifier of this relationship is not yet established. This study will extend to establish the relative contribution of alcohol-use disorders in the balance of circulatory pro- and anti-inflammatory cytokines in humans. We hypothesize (in upcoming study, using the material collected during this study) that ethnicity moderates such relationship. We intend to compare the findings between Nepalese data and data from comparable Norwegian clinical population.

1.3 RATIONALE FOR THE STUDY

Although many epidemiological studies relating to substance use and psychiatric disorders have been conducted in the western world, the methodological applicability and extent of generalisability of such studies in the third world context is questionable. So far no comprehensive studies have been conducted in Nepal to address the comorbidity associated with alcohol-use disorder and other psychiatric disorders. Even less is known about the characteristics of the very few patients who actually seek treatment. It is necessary to investigate them in order to get insight of the disease epidemiology in population level. Absence of pertinent baseline data, phenomenon of treating the patients in this group as 'miscellaneous' and lack of specialized treatment modalities for dual diagnosis patients created a ground for this study in Nepal. In addition, the complex socio-cultural attribution (including taboo attached with alcohol dependence and depression) and poor health economics make Nepal a unique ground for alcohol related psychiatric disorders.

Furthermore, epidemiological transition following the rigorous socio-political transformation of the society in the past decade necessitates an observation of psychiatric comorbidity against which future findings may be compared. The rationale for undertaking this study are simpler than complex. Both alcohol-use disorders and depression are common conditions, their share to morbidity and mortality is quite high, and the share of South Asia in non-infectious diseases (besides infection and malnutrition) has appropriately been characterized as a coin of the double burden. The comorbidity of alcohol and related psychiatric illness increases the morbidity in geometric fashion. The theoretical and clinical implication of this study is manifold. The first step is to scale the extent of the problem and bring in attention from stakeholders, mainly the health policy makers and service providers. It is equally necessary to contribute to the scientific community by sharing the findings from relatively new but naturalistic (in the sense of culturally ambivalent drinking society) setting for substance abuse research. Hence, the theme of this study in Nepal is rather important and emergent.

1.4 Research Questions [2]

1. How prevalent are major depression and anxiety disorders among individuals who seek treatment for their drinking related problems in alcohol treatment units in Kathmandu, Nepal?
2. How are sociodemographic and clinical characteristics related with comorbid depressive and anxiety disorders in this population?
3. Are the prevalence and correlates of comorbid anxiety and depression disorders different across two strata of Nepalese society divided by socio-cultural taboo on alcohol use?
4. How common are nicotine and other substance use among alcohol abusing population in Nepal who seek treatment for their problem drinking?
5. How are suicidal ideation, plans and attempts made by alcohol using population related to the alcohol consumption pattern and comorbidity of major depression/anxiety disorders?

1.5 OBJECTIVES

1.5.1 General Objective

To estimate the prevalence of major depression and selected anxiety disorders among alcohol abusing or dependent population who seek treatment for their problems associated with drinking, and to observe the socio-demographic and clinical correlates of such comorbidity in the context of Nepal. To find association of alcohol-use disorders with comorbid depression/anxiety, suicidality, and other substance use disorders in alcohol-restricting and alcohol-banal divides of the same society.

1.5.2 Specific Objectives

- To find out the prevalence of major depression among Nepali population who attend treatment centres for their alcohol-use disorder.
- To find out the prevalence of social phobia, agoraphobia, generalized anxiety disorders, panic disorders, and a history of post-traumatic stress disorders among Nepali population who attend treatment centres for their alcohol-use disorder.
- To establish how socio-demographic parameters, including age, marital status, ethnicity, occupation and urbanity of their place of origin relate with such comorbidity.

[2] Paper I addresses research questions 1-3, considering depressive comorbidity only.

 To find out if belonging to a social class that has a taboo against alcohol use is a predictor of comorbid depression/anxiety disorders/suicidality/other substance use disorders.

 To find out if levels of serum γGT, CDT, EtG, EtS, or urinary EtG, among other biological measures correlate with presence of a comorbid psychiatric disorder, major depression in particular.

CHAPTER 2. METHODOLOGY

2.1 Overview

This cross sectional study from one tertiary level hospital and seven alcohol treatment centers from central Nepal investigated 188 institutionalized patients with an alcohol-use disorder by using comprehensive interview schedules and biological tests to assess anxiety and depressive comorbidity. Lifetime and 12-month prevalence rates of major depression and selected anxiety disorders comorbid with alcohol-use disorders were estimated. Socio-demographic and clinical correlates were examined by classifying the population into traditionally alcohol consuming community and the community that has social restriction or taboo against alcohol use.

2.2 Study technique/design

The inception of this study was based on positivism. Thus we endeavored to measure prevalence of our outcome variables in the background of testable hypothesis that would lead to ascertainment of their association with explanatory variables (sociodemographic, clinical, and biochemical). We recognize that certain aspect of the study could have been performed by a qualitative method, since a vast majority of mental disorders can be seen as a result of social construct. An ethnographic approach to understanding the mediatory role played by certain factors, such as social taboo, triangulated with epidemiological method could be a desirable alternative approach as used by Kohrt and colleagues (22). We were guided by the concept that an objective system of measurement generates facts and the hypothesis that social attribution has an impact on the rates of depression could be tested (93). Thus, a quantitative research technique was chosen in order to quantify the size, distribution of and association between the study variables.

The study was carried out with a cross-sectional design. A cross-sectional design is commonly used in epidemiological and clinical studies where the measures of interest are exposure and outcomes that are measured at a point in time. The study objective favored this design due to the fact that current and life time occurrence of major depression and anxiety disorders, substance use disorders, and suicidal behavior together with their sociodemographic and clinical states could be assessed simultaneously. We intended to compile the historical occurrence of the variables of interest at one point in time. This retrospection has its own peculiarities, which will be discussed later. Conversely, the study

theme could be operationalized and carried out by using longitudinal designs. For example, prospective longitudinal study design could be helpful in observing the incidences of depression and anxiety disorders over a time span. Similarly, a cohort of pre-pubertal children in the study area, for example, could be followed up over many years to observe the occurrence of the outcome measures. Given the resource limitations in terms of manpower (requiring trained interviewers), time (four and half months available for the whole data collection), limited funding pledges (against costly laboratory tests), a cross sectional study design was considered the most suitable undertaking.

This study can be regarded as a descriptive diagnostic and analytical study of clinical population. The diagnostic measures are aided by the use of fully structured psychometric tools. The analytical part is accomplished by analysis of biological/biochemical parameters.

2.3 Sampling

2.3.1 Study area and population

The Kathmandu valley is a cultural, political and commercial hub of Nepal with 1.5 million inhabitants (8). It represents the urban concentration of the whole country with relatively better indices of development. Besides the ethnic Newars, Kathmandu harbors people hailing from different parts of the country with diverse religious, cultural and ethnic backgrounds. Most of the country's specialized health centers are located in the same region. Kathmandu is a preferred centre for health care.

Fig 2: Map of Nepal showing recruitment districts (94)

According to unofficial sources (official data not available), of some 75 rehabilitation centres running in different parts of the country, 25 were operating in Kathmandu valley. We conveniently selected one hospital which offered pharmacological treatment and seven rehabilitation centers which offered non-pharmacological rehabilitation care from different locations in Kathmandu and Lalitpur (Patan) districts (Fig 2).

The department of Psychiatry at the Tribhuvan University Teaching hospital (TUTH) in Maharajgunj, Kathmandu ran a 'de-addiction ward' where patients diagnosed with one of substance dependence syndromes were admitted to detoxify them, generally over a period of two weeks. Majority of the patients were enrolled either from the Psychiatric outpatient clinic or from the Emergency unit. Some of the patients were also referred from other departments at the same hospital. A team of psychiatrists and clinical psychologists provided benzodiazepine based detoxification followed by psychological counseling services.

The remaining seven institutions offered residential rehabilitation care for an average of three months. Peculiar about these centers was that all of these constituted therapeutic communities and no drug was allowed for detoxification purposes. However, most of the centers had visiting psychiatrists or general practitioners who, on an absolute need-basis, sanctioned pharmacological treatment of chronic conditions including some psychiatric disorders, rather than detoxification purposes. Some of the centers provided multivitamin supplement to the clients, some even extended psychological counseling services. All centers were run by counselors who had either received training or had working experiences in their field for a varying duration of time, others were recovering volunteers. Richmond Fellowships Nepal (Alcohol) offered rehabilitation care explicitly for alcohol users, whereas Richmond Fellowship Nepal (Female) was the only center providing services for female alcohol users. Other centres, namely Ashara Sudhar Kendra, Nawakiran Rehabilitation Centre, Prarambha Nepal Rehabiliation Centre, Richmond Fellowship Nepal (Male drug unit), and Clear Vision Drug and Alcohol Treatment Centre enrolled treatment seeking male substance users- including the alcohol users. All the centers were applying the principles of 12-step programs. Such establishments required license from the Ministry of health and Social Welfare Council, but no official data could be obtained regarding the number of the operational centers.

Of the 11 visited centers, two refused to participate and other two were excluded. Details are mentioned in the section *sample attrition*.

Patients receiving treatment on outpatient basis were not included because it would be ethically incorrect to ask them wait for a length of hours to contribute to the study. It was also necessary to create uniformity in the nature of study participants. Selective exclusion of these potential participants was not a part of our intention, as highlighted in the study protocol. Patients under current influence of any substance as judged clinically were deferred enrollment. All potential participants were screened for psychotic features before request for participation was made. In order to minimize the overlapping symptoms of alcohol withdrawal and axis I disorders, the interview schedule was optimized for a longest possible duration of abstinence from alcohol use. No interviewing was done until 10 days of abstinence was ensured. Institutional stay length was considered a valid period of abstinence. However, one potential participant at the hospital was identified alcohol smell positive, and therefore excluded.

No clear difference in socio-demographic characteristics was noted between treatment seekers at the hospital and those at the rehabilitation centers. However, patients who developed delirium tremens, and more plausibly those with alcohol use related physical ailment, were more commonly taken to the hospital rather than to one of the rehabilitation centers. The centres for treatment were chosen voluntarily and the service charges depended on the patients' out-of-pocket expenditure. Inpatient treatment at the hospital for a fortnight would cost around 5000 Nepalese Rupees (USD 1 =approximately NRS 72 as of May 20, 2011), whereas the rehabilitation centers charged between 24 thousands and 36 thousands Nepalese Rupees for the 3 month-long residential care. Fig. 3 shows the contribution of participants from these centers.

2.3.2 Sample

The above-mentioned treatment units constituted the study sites; all clients undergoing residential treatment at one of these units (and in generalization, other treatment centres that resemble these units) with a primary reason for treatment seeking being alcohol use related but not primarily physical ailment made the study population; each client meeting the inclusion criteria were study subjects. The sampling method can be attributed to clusters of sampling units of these treatment centres chosen conveniently, and study participants were

inclusive rather than random. The methodological limitations of non-probability sampling employed in this study are discussed later.

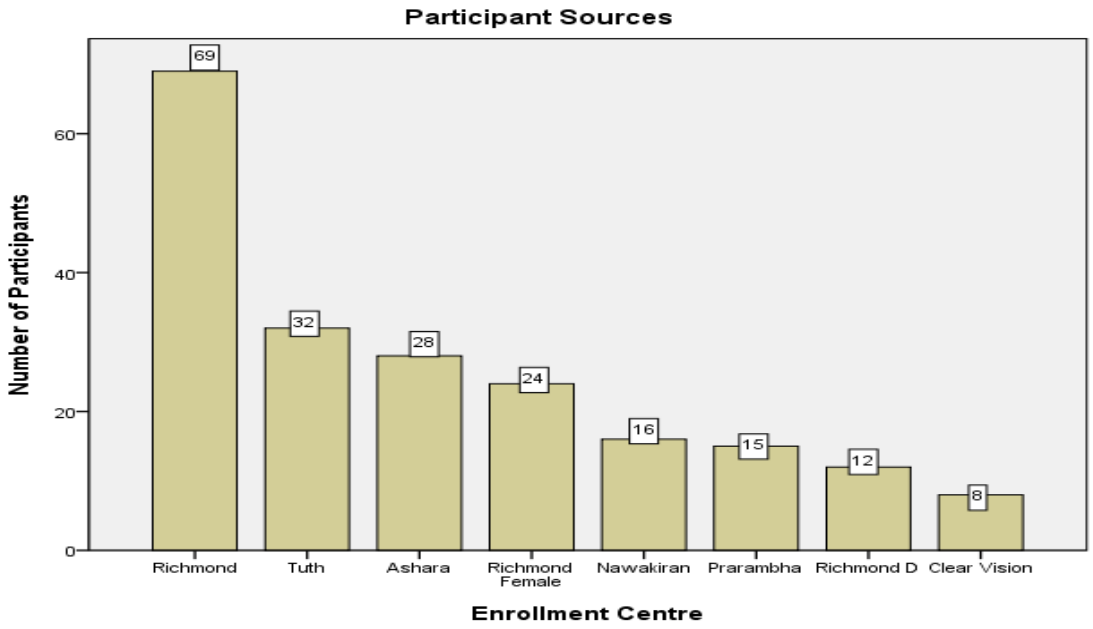

Fig 3. Sources of patients who agreed to participate (N=204) in the study. Note that 5 patients dropped out of the treatment before the interview could be taken. Tuth stands for Tribhuvan University Teaching Hospital. All others are rehabilitation centres.

Only four and half months were available for data collection, and the flow of patients meeting inclusion criteria in any of the treatment centers in the study area were under 20 at any time which compromised the size of enrollment. Thus, convenience method of sampling was chosen. This implied visiting several of such centers and recruiting participants as they became available. Thus our sample constituted of consecutively admitted patients at the treatment units during the data collection period of 17th August and 28th December 2010.

The aim of the study is not to suggest a causality or direction of alcohol-use disorders and MD or anxiety disorders which is better approached with a longitudinal study design. We wanted to observe the strength of association between various socio-demographic and clinical characteristics of the patients that might have bearing in the comorbidity. This did not necessitate randomization. Studies like this might be approached with a case control design, but since we would also have non-depressed AUD patients, we were left with the possibility to observe the differences, for example, between the two groups of depressed and non-depressed AUD patients. This study hence justifies the method chosen for epidemiological

observation of psychiatric comorbidity. We believe that this study would be useful as a baseline against which the insights of the gravity of alcohol-use disorders and associated comorbidity can be acquired, extending into general population level.

2.3.3 Sample Size and Selection

No convincing data on proportion of axis I psychiatric diagnoses among alcohol users were available from Nepal. Therefore, report of a study but done in American population which estimated the 12-month prevalence of MD among treatment seekers with an AUD in the preceding 12-month period at 33% was used as a best guess (19).

A prevalence proportion (p) of major depression among the clients was considered 0.33. The target sample size was determined using formula for precision of proportion for the comorbid to isolated alcohol-use disorder:

$$N = \frac{1.96^2 * p(1-p)}{d^2}$$

For a 95% confidence interval for p that is expected to be about 33% or (0.33) with a margin of error (d) no more than 0.05, the number of subjects (N) required would be $\frac{1.96^2 * 0.33(1-0.33)}{0.05^2}$ ≈ 340. However, only 199 participants completed the interviews. This would compromise confidence interval by 2%. As is frequently the case, studies of this nature suffer statistical power. We argue that the power of the study would be enhanced by its capacity to include a majority of the clients that sought treatment. Rather than the number of study participants, the strength of this study was in the inclusive nature of participants who represented diverse socioeconomic status, ethnic backgrounds, and place of origin. These treatment centres can be considered catchment units for the whole country (Fig 4).

All clients present at the institution during the data collection period and who met inclusion criteria were successfully enrolled from all the participating institutions except for Ashara, Richmond D and Clear Vision rehabilitation centres. The contribution of these centres in total participation was under 24%. The supporting staffs at these institutions were asked to make a list of available clients and the researcher approached the client in descending order of recency of admission. Thus participant selection was inclusive wherever feasible, and purposive wherever not feasible, but the basis for selection of study sites was entirely convenience. Government authorities were not able to provide data on the number of operating centers and patient flow in the institutions of the region; hence sampling frame and representativeness of the centres couldn't be ascertained. Despite this, it was known that

outside hospital settings, Richmond Fellowship Nepal (Alcohol), which made a third of our sample, was the sole center in the whole country dedicated specially for rehabilitation of problem drinkers.

Fig. 4 Map of Nepal showing all 75 districts. Flagged regions are the districts from where the participants originated. Two flagged zones are outside Nepal to represent the country of residence in the preceding 5 year period. Scale is not applicable. Map source: World Wide Web (95).

2.3.4 Study groups

One of the main aims of the study was to observe the difference in the groups in a naturalistic setting, where Nepalese society is divided in ambivalence regarding the use of alcohol. Fig 5 depicts the proportion of the participants who belonged to the alcohol related tabooed group (Tagadhari) and non-tabooed group (Matwali).

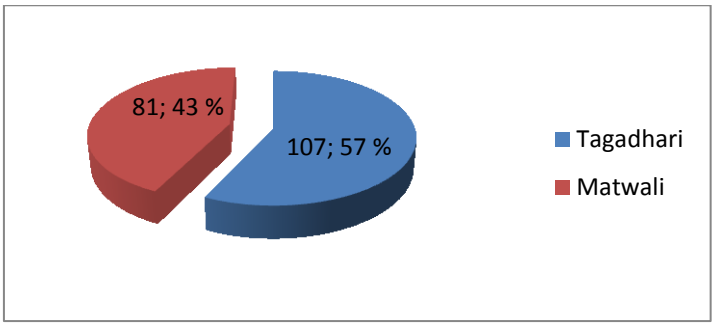

Fig 4. Groups of participants divided according to taboo on alcohol use.

2.3.5 Sample attrition/bias

The method for study sites selection has been discussed in the section Study population. Of the visited 11 centers, 2 refused to participate and other 2 were excluded. One center which reasoned organizational restructuring for non-participation was found to have 4 patients with alcohol use related problems at the time of approach. The centre lied in the vicinity of another participating centre. The centre was led by a recovering alcoholic who had undergone (and practiced 12-step philosophy himself) at yet another rehabilitation centre included in our study. Another centre which pointed confidentiality concerns behind non-participation contained 17 patients at the time of approach with unknown share of alcoholics. The director of the centre was away at the time of approach. Reattempt for request for participation was not done because there were adequate possible samples available for recruitment given the resource limitations. There were no obvious differences in the characteristics of the clients at these centres compared with the centres from which recruitment was done. But this assumption may not be reliable.

One centre was excluded because of its location about 20 kilometers from the laboratory where samples were processed - it could not be feasible to process the samples within two hours after collection. Yet another center was excluded because it applied a different philosophy (Sauna bathing, use of high dose vitamin supplement, and course teaching) and the treatment cost was over five times higher than all other centres - thus distinguishing the clients from the rest of the sample.

Five participants who signed the consent form dropped out of the rehabilitation programs before the scheduled interview dates. Among them were three females who absconded and two males who had left against institutional advice. Furthermore, there were 11 refusals for participation. Two patients were from hospital; one of them cited disagreement from his family, and the other postponed the decision until the discharge. We were unable to follow him. There were two other patients at the hospital who met the conditions except for the physical inability to participate. All nine clients from the rehabilitation centres who refused participation reasoned non-interest. We assume that the potential influence this could make in our results were non-significant. The response rate calculated was 95.2%for all requests. However, of all considered 221 participants, the participants included in final analysis (188) made 85%.

Biological sampling details are given in a separate section.

2.3.6 Eligibility Criteria

Before recruitment in the study, all the selection criteria were reviewed by the researcher himself. Persons who met all the following criteria were considered eligible to participate in this study:

1. Age 14 years or older of any gender.
2. Written informed consent signed by the client (signature of a witness to confirm informed consent together with the thumb prints in case of illiterates).
3. Be a returning/follow up or new patient admitted with a diagnosis of alcohol dependence syndrome or poly-substance dependence syndromes (with alcohol abuse or alcohol dependence) at the 'de-addiction ward' of TUTH, or an in-house client at one of the participating alcohol and/or drug rehabilitation centers whose main reason for such admission was problem drinking.

2.3.7 Exclusion criteria

Persons were excluded from participation in the study even if they met the above criteria if they met any of the following:

1. Unable to complete the interview due to ill health.
2. Unable/refuse to consent for any reasons.
3. Under the influence of recent alcohol or other substance use as judged clinically.
4. Presence of any substance withdrawal delirium (DSM-IV; see appendix).
5. Disorientation or ongoing psychotic symptoms.

2.4 Ethical Considerations

Given the sensitivity of the topic, socio cultural acceptability of the questioning, and vulnerability of the study population, ethical considerations were given high emphasis. Participants were institutionalized individuals for treatment to their problem drinking, either brought by self motivation or in compliance with suggestions from care takers, often family members. However, the female participants from refugee camps in Eastern Nepal were brought with the support of International organization for Migration.

Early in the process of project planning we anticipated several potential vulnerabilities borne by these individuals. Among these vulnerabilities included psychological distress as part of manifestations of potentially multiple neurotic or psychotic, or both pathologies. A subpopulation would be multiple substance users. We anticipated history of criminal

behaviour, among other personally sensitive issues. During the recruitment period, it became trivial that many of them were socio-economically disadvantaged. Patients with traumatic antecedent events with certain diagnoses of anxiety disorders and suicidality might be posed to retraumatization due to certain sets of questions. Moreover, participants contributed with their time and personal information and also provided blood sample for investigation demanding the justification of benefit over potential harm in such clinical researches. We employed measures to limit undesirable effects. These measures are discussed further below.

Patient's autonomy was given first priority. Written informed consents were taken before the interview session started and verbal re-consenting was requested before administration of every new instrument. A separate question was placed on the written consent regarding the collection of blood and urine samples. The participants got the choice of contributing to the study without offering biological samples. The samples alone were not collected since a lack of diagnostic assessment would make the samples 'orphan'. The rates of acceptance are given in the materials section. All voluntary participants were informed of possible risks and benefits of participating in the research in clear and comprehensive tone at least twice. We conducted group sessions at the institutions where the principal investigator discussed relevant clinical aspects of addiction and responded to questions raised by the clients. This comprised of lecture on the biological domain of addiction, its entity as a disease phenomenon, possible effects on the body and the treatment. The same opportunity was used to invite them for participation in the study. However, group sessions were not possible in the case of hospital due to short treatment duration (2 weeks or less) and low occupancy rates (5 or less number of clients at any given time during the study period). These patients received invitation for participation before the interview was scheduled.

All the interview sessions were timed and a refreshment break was made after 45 minutes if the questioning was not yet complete. Wherever a separate appointment was made for the interview, reimbursements were offered for transportation costs limited to a maximum of Nepalese Rupees 250 (1 Nepalese Rupees as of May 20, 2011= 0.014 American dollars). We weighed this would not amount to aggravating risky behavior or manipulative phenomenon because it was minimal, was supplied as reimbursement and paid as an expense incurred for the sake of participation. Participants received free general physical examination after the interview session from the principal investigator, if so requested.

All maneuvers, including physical examination, and the venepuncture for blood sample collection were done at the presence of the duty manager or counselor at the institution. But interviewing was done in privacy except in case of three female participants who upon inquiry chose to have an attendant beside. Those participants were accompanied by a supervisor at the institution during interviewing. There was, however, also a male participant who wished to be accompanied by his wife during the interview; this request was accepted.

The use of alcohol and other illicit substances in the society constitutes sensitive personal information and might potentially trigger judgments on an individual's behavior which could be detrimental to his/her social wellbeing. As the questionnaire involving depression, anxiety and suicidality might cause discomfort to the participants, utmost care was given not to overwhelm them from the questioning. The modules with sensitive questioning especially the suicidality section of CIDI were carried out towards the end. Three participants showed emotional outbursts, hence the interviewing was stopped. They opted to complete the questionnaire in the next session, which was then planned in their convenience.

For participants leaving the direct observation of clinician within the day of the interview session was evaluated and consulted with the attending or a duty clinician/psychologist before discharge. All the participants were assured the option of quitting the session any time during the interview. Any question that the participant did not feel like answering was given option to skip. Moreover, confidentiality and privacy of any personal information and their mental integrity as highlighted in the declaration of Helsinki (96) were respected. Data handling procedure is discussed in a separate heading in the methodology section.

All the interview sessions took place in a private cell ensuring confidentiality, safety and comfort. In addition, relevant counseling was provided at the end of the session to the patient who sought medically pertinent information. This dual role as a researcher and a clinician was however balanced by not making any prescriptions.

Another important ethical consideration to be made in the study was anonymity. For participants who wished to be contacted for results of the study required their contact details to be recorded. The investigator did so by coding in the response forms which could be decodable only by him whenever necessary. Each participant was given a unique identity number, and personal identification details were placed separately. All the response forms

were stored by the researcher at his residence during the data collection period. Later, all the response sheets were brought on hand luggage with the investigator. All paper data were then locked up at SERAF, the consent forms were stored at a separate locker at SERAF.

The serum samples were consequently destroyed after the aforementioned investigations. One set of serum samples are still being preserved with the extension permission from the relevant ethical review boards. These samples will be analyzed together with samples from Norway for investigation of serum cytokine levels. Details are given in the section *Biological parameters.*

The ethical consideration was thus in compliance to the following principles set by internationally recognized guidelines for the ethical conduct of medical research with humans: autonomy, non malfeasance, beneficence, and justice (97;98).

2.4.1 Ethical Review

Before the start of the data collection, the ethical review and clearance were obtained both from Norwegian regional ethics committee (REK) Region South-East and Nepal Health Research Council (NHRC). The institutional review board at the Tribhuvan University Teaching hospital was also applied for ethical review. The committee failed to provide such an approval owing to complex nature of the study in concern, but validated the review from the NHRC which is the governing body of all institutional review boards in Nepal. Since we intend to include the Nepalese data for cytokine testing, we applied for extension of retention time for the biological specimens, an application was sent at the REK, which has extended the date for three years (see appendix).

2.5 Assessment

2.5.1 Psychometric Instruments

A myriad of tools have been developed to diagnose and measure severity of psychiatric conditions. Choice of the tools was made with consideration of earlier use, validation done in the population in concern and the circumstance of their use in research. Self Reporting Questionnaires (SRQ) have been used in various settings to screen effectively mental symptoms in the community but it will not be practical in this population because the average

literacy rate of Kathmandu which was among the highest in Nepal is at 83% (8). The tools used in the present study were structured diagnostic interviews or screening tests for harmful alcohol use and mental distress.

The following tools were used in course of this study.

1. Hopkins Symptom Checklist-25 (HSCL-25) Nepali version: This was initially developed by Derogatis et al. in 1974 and has been used widely in different settings as a measure of psychological stress (99). This is a screening questionnaire with 10 items on anxiety and 15 on depression symptomatology. All items have 1-4 response set to evaluate their anxiety and depression status. The scoring is done on each answer according to the frequency of symptoms experienced (1=not at all, 2=a little, 3=quite a bit, 4=extremely). The anxiety and depression scores are average scores of all items divided by the number of items within the respective subscale (10 on anxiety and 15 on depression), with higher scores indicating greater mental disturbance from anxiety and depression. The HSCL-25 has previously been validated (33) and used for the Nepali population (33;100). In the present study, answers were marked for all the questions, but two questions in the depression module were excluded from analysis due to high rates of acquiescence responses. These questions dealt with blaming oneself for all kinds of mishappenings, and feeling of being trapped or caught in something, probably germane to the in-treatment substance users as participants.

2. Alcohol-use disorder Identification Test (AUDIT): The AUDIT was developed by WHO as a simple method of screening an individual with three questions about hazardous alcohol use, three about dependence symptoms and four about harmful alcohol use (101). It is scored as 0-4 with 5 answers on first 8 questions with higher values representing higher frequency. The last two questions, alcohol related injuries and others concerned about drinking, are responded as 0(no), 2(yes, but not in the last year), and 4 (yes, in the last year). This tool has enjoyed widespread use in clinical and research settings, including demonstrated psychometric properties in a similar population (102). It was also used in earlier research in Nepali language, in clinical and research settings**.** Research has been conducted in a wide variety of countries and cultures suggesting its applicability as an international screening test (101). The average score of 8 and above has been identified as cut off level for both sexes as alcohol problems; 8-15 medium level of alcohol problems and ≥16 is high level

alcohol problems and ≥20 possible alcohol dependence warranting specialized evaluation (103).

3. Timeline Follow back (TLFB-Alcohol): First coined by Sobell et al. (104), the TLFB is a method for assessing recent drinking behaviour by asking clients to retrospectively estimate their daily alcohol consumption over a time period ranging from 7 days to over 24 months prior to the interview. The tool is useful in examining variability (i.e., scatter), pattern (i.e., shape) and extent of drinking (i.e., elevation; how much) (104). A Nepalese calendar from the last 30 days was used to assess the drinking behaviour. Quantification of drinks was made by using a chart for different kinds of drinks on use in the locality (see also definition section for unit measurement). The reason for using this tool was to substantiate the findings of biological parameters: in order to observe the correlation between the GGT, CDT, EtG levels and the pattern of alcohol use in the past weeks.

4. Composite International Diagnostic Interview (CIDI) (105) version 2.1 (Nepali): This is fully structured comprehensive interview to be used by trained interviewers for the assessment of mental disorders according to the definitions and criteria of International Classification of Disease (ICD-10) (106) and DSM-IV (107). The modules used in this study have shown acceptable reliability and validity in a number of studies across a wide range of cultures (108;109). The investigator who also received training for its use carried out the interviews. The tools have been previously translated into Nepali using standard procedures (84) and used previously among Nepali speaking Bhutanese refugees in Nepal (34). The following sections of CIDI were administered:
    a. Alcohol Use (AU)
    b. Illegal Substance Use (IU)
    c. Depression (D)
    d. Agoraphobia (AG)
    e. Generalized Anxiety Disorder (G)
    f. Panic Disorder
    g. Post-traumatic Stress Disorder (PT)
    h. Social Phobia (SO)
    i. Suicidality (SD)

5. Investigator formulated question for measurement of satisfaction with the offered treatment were administered at the end of the interview session. It included a separate questionnaire recording chronic illnesses, significant medical/surgical history, and smoking history- both lifetime and current (see appendix). Demographics section included one extra question that asked about availability of significant other who could offer moral, economic or logistic support when sought (answered as inadequate, some, adequate).

2.5.1.1Preparation of tools: While all other sections were used from available Nepalese versions of CIDI, the two sections, Suicidality (SD) and Illegal Substance Use (IU) were extracted from English version of CIDI 2.1. The standard guideline for the translation of these tools was followed, and the procedure was repeated as mentioned elsewhere (84). In short, SPN translated the questionnaire into Nepali. Another non-psychiatric specialized medical doctor back translated the forms into English. This was reviewed by an expatriate mental health researcher and Psychiatrist who had worked extensively with transcultural psychiatry, had used CIDI earlier with Nepalese people. He identified and suggested amendments were discussed to make the final version. This process was done for two section, i.e Suicidality and Illegal substance use only. A repeated focus group discussion for increasing the understandability of these questionnaires as suggested (84) could not be done because we anticipated heterogeneous group of people in terms of culture, ethnicity and language of daily use.

All the psychometric tools were pen and paper version and administered in Nepali language except in case of one patient who chose to be interviewed in English since he was non-native Nepali speaker. Multiple tools were used in order to increase the accuracy of the corresponding measures and to substantiate the findings of other tools.

2.5.1.2 Pretesting of the tools: Pretesting was done in the first month of field visit while waiting for the approval from the review boards. The whole batteries of instruments were pretested on two patients from the hospital, and 3 from one of the rehabilitation centres who would meet criteria for inclusion. The questionnaires were modified according to the observation from pretesting. Questions that returned high rates of acquiescence responses were dropped from analysis only.

The psychometric instruments used in this study are attached in the appendix. CIDI questionnaires are not found in appendices because of copyright permissions limited to WHO.

2.5.2 Biological Parameters

A number of biomarkers have been investigated in an attempt to verify objectively the history of alcohol use especially in recent past. Since it is necessary to complement the accuracy of the psychometric tools, in diagnosing and characterizing alcohol-use disorder, the following laboratory analysis were carried out in the study subjects:

Serum analysis

1. Carbohydrate deficient Transferrin (CDT)
2. gamma-glutamyl transferase (GGT)
3. Ethyl glucuronide (EtG); Ethyl sulphate (EtS)- reporting awaited

Urinalysis

1. Urinary pH
2. Urinary Creatinine
3. Urinary EtG

Other serological tests were planned in connection to an evolving research project DARCY. This study will investigate the differences in the cytokine profiles of depressed and non-depressed substance users against the healthy controls. The tests include pro-inflammatory cytokines: IL-1, IL-6, TNF-α, and INF- γ. Anti-inflammatory cytokines considered are IL-4, IL-10, and IL-12. This was planned at the early phase of the current study in which we attempt to find the ethnic differences (Nepalese and Norwegian samples) in the relative balance of pro-and anti-inflammatory cytokines in the backdrop of AUD-MD comorbidity.

2.6 Socio-demographic Characteristics of study population

To answer question regarding the socio-demographic correlates of the outcome variables, a separate questionnaire (modified from demographics section of CIDI 2.1) was formulated by the investigator and administered at the start of the interview session. The characteristics noted were as follows.

a. Gender: Male/Female/Other
b. Age: noted in scale; further stratified on groups: 14-22/23-35/36-55/ 56^{+}
c. Urbanity of origin: urban/rural
d. Urbanity of residence: urban/rural

e. Ethnicity/Caste: Dichotomized into Matawali or Tagadhari noting Brahmin, Chhetri, Newar, Tamang, Rai/Limbu/Gurung, Sherpa, Madhesi or other and confirming with the participants whenever not obvious.
f. Marital status: Never married/married and cohabiting/ divorced or living separately or widowed /other
g. Type of family (Nuclear/Joint/Extended) and number of children
h. Education : Highest level of education attained: none, some school (up to 7 years or attended adult education), secondary (8-12 years), University
i. Occupation: unemployed/cottage industry/ farmer/service (private or government firms)/own business/labourer/foreign employment/drivers
j. Social support (moral and/or logistic when needed): none, some, Adequate.
k. Significant other (if any: relation to the participant)

Of the 198 completed interviews, almost 90% were males and less than 15% were hospital attendees. Patients were aged between 14 years and 64 years with a median age of 35 (SD: 10.1) years. Over two third of the sample was aged between 24 and 44 years. There were about 29% born and living in rural areas, wheras 55% were urban dwellers. About 15% of the participants had moved from rural to urban location for at least past 5 years. A half of the sample, 97 were based outside the Kathmandu valley; 18 (including 10 Bhutanese refugee women) were foreign born. Nine were repatriates. In all 108 (55%) of the sample belonged to upper caste Brahmin or Chhetri, followed by Newars (41) and Mongoloids (36). Fortyeight participants had never married, 28 were divorced or living separately, whereas the rest (62%) were cohabitating in marriage. Two third (128) of the participants were parents. As many as 57 (28%) had less than 7 years of formal education -of them 16 were illiterate, 37 (19%) were university graduates. One hundred and eleven (56%) were living in a nuclear family setup, while 13 (7%) reported their family as broken or living alone. A half (96) of the participants had a stable source of income (white collar job or own business), 18 were students and another 32 were unemployed, 30 were driver, unskilled laborers or returnee from foreign employment. Almost a third (62) had below average income levels, and 54 of them reported of not receiving adequate social support in terms of moral, economic or logistics when sought for.

2.6.1 Alcohol use related characteristics: A majority of the sample (N=107; 54%) self identified as belonging to the social class that has taboo on alcohol use (Tagadhari). Locally brewed Raksi was the most preferred drink (47%) followed by sealed spirits (43%); less than

10% reported beer, wine or locally fermented Jand or Tongba as drink of choice. The mean career of habitual drinking was 16.8 years (SD 9.8). Nearly three fourths of the sample admitted of drinking 4 or more days per week; only 5% admitted drinking monthly or less frequently. About 75% had used alcohol as eye-opener sometime in their drinking career, and 60% had experienced alcohol-induced blackouts.

2.7 Definitions and Variables

2.7.1 Definitions

Definitions of all the diagnoses were made according to DSM-IV or ICD-10 criteria. Cutoff values, whereable applicable, were defined according to standard recommendations for respective tools. Our main outcome variables were measured as alcohol abuse, alcohol dependence, major depressive episodes (life time/ past 12-month), social phobia, agoraphobia, panic disorder (with or without panic disorders), general anxiety disorders, post traumatic stress disorders, and suicidal ideation/plan/attempt (lifetime/past 12 month/current) as shown on table 3. Measures of ethanol concentration and units were contextualized with the help of translated version of CIDI section J, where the available drinks were standardized during the preparation of the instruments in 1997. Unit measurements of locally available drinks were operationalized as under:

Beverage type	**Volume/Concentration**	**Units of Alcohol (standard drinks)**
Beer	1 bottle (650 ml) ~3.5-5% 1 can (330 ml)	2 1
Wine	1 glass (100 ml) ~12%	1
Vodka/Rum[§]	1 quarter	4
	½ bottles	8
	1 Full (1 bottle of 750ml) ~40%	16
Jand /Tongba*	1 mana (0.55L) concentration unstandardized	3
Raksi[#]	1 glass (0.2L) (?~20%) concentration unstandardized	2

Table 1. Alcohol units operationalized according to beverage type *=Local fermented drinks (usually as food item) [#] =Locally distilled drink; [§]= calculation not compatible with neat drinks.

2.7.2 Dependent Variables

Variable	Measure	Source
Alcohol-use disorders • Alcohol abuse • Alcohol dependence	CIDI (section J, alcohol use) Criteria: DSM-IV (American Psychiatric Association)	(CIDI core version 2.1 Nepali (WHO)
Depression	Average Score from HSCL-25 (1.75 for both genders) (33)	HSCL-25 (Derogatis et al., 1974)
Major depressive episodes	CIDI depression module	CIDI core version 2.1 Nepali (WHO)
Anxiety	Score from HSCL-25 (1.75 for both genders) (33)	HSCL-25 (Derogatis et al., 1974)
Anxiety diagnoses • Social phobia • Agoraphobia • Panic disorders • GAD	CIDI anxiety modules	CIDI core version 2.1 Nepali (WHO)
PTSD	CIDI PTSD module	CIDI core version 2.1 Nepali (WHO)
Substance use disorders	CIDI (Illegal substance use)	CIDI core version 2.1 Nepali (WHO)
Suicidality • Lifetime ideation	CIDI suicidality module	CIDI core version 2.1 Nepali (WHO)

• Lifetime plan • Lifetime attempts • 12-month ideation • 12-month plans • 12-month attempts		

Table 2. Dependent variables ; PTSD= Post-traumatic stress disorder

2.7.3 Independent Variables

Variable	Measure	Source
Demographics	Age, gender, Ethnicity, Urbanicity, marital status, family type and size.	Created for study
Education	Highest level of formal education attained (none, adult education/ some school (upto 7 years), secondary (8-12years), University)	Ordinal scale created for study
Employment	Type of occupation (unemployed/cottage industry, farmer/service (govt./Pvt.), own business)	Nominal scale created for study
Social support	Availability of People close enough to support (significant other): family/ relative/organizations morally and/or logistically when needed.	Ordinal scale created for study
General Health	Chronic illnesses (Yes/No, particular) Surgeries under GA* (Yes/No, particular) Long term medication (Yes/No, particular) Smoking cigarette/*Bindi* (Yes/No,duration/?current) Tobacco chewing/*hukka/tamakhu*(Yes/No,duration/?current) Ambition in life (Yes/No, particular)	Created for study
Problem drinking in first or second degree relative	(Yes/No, relation(s))	Created for study

Satisfaction	Categorical values 0-4 on likert sclae	Created for study
Biological markers#	Serum analyses: 1. Carbohydrate deficient Transferrin (CDT) 2. Gamma glutamyl transaminase (GGT) 3. Ethyl glucorunide (EtG)-reporting awaited Urinalysis: 1. Urinary pH 2. Urinary Creatinine 3. Urinary EtG	

Table 3. Independent variables (#=also usable dependent variable in some analyses) *GA= General Anesthesia

2.7.3 Other explanatory variables

Alcohol consumption	Days in last 30 days: consumed alcohol units (Timeline follow back: TLFB)	Sobell& Sobell.,1995
Alcohol problems Medium level alcohol problem High level alcohol problem Possible alcohol dependence	A total score of 8 + on AUDIT to identify hazardous and harmful drinking 8-15 on AUDIT ≥16 on AUDIT >20 on AUDIT	AUDIT (WHO, Saunders., 1993)

Table 4. Alcohol use related variables

2.8 Data Collection

Data were collected using standardized interviewer-administered surveys. The investigator who had also experiences of clinical practice in the same area and had undergone training from an authentic WHO CIDI trainer in Norway conducted the interviews. Expertise on the administration of the psychometric instruments were ensured by practical exercises at Innlandet hospital trust, Sanderud, Hamar and the Norwegian centre for addiction research (SERAF) before field trip.

2.8.1 Recruitment

The researcher visited the hospital every working day. He checked the patient register for potential participants, who were then approached personally at the 'de-addiction unit' of the hospital. The researcher introduced himself according to the details mentioned in the beginning of consent form (appendix). They were checked for capability to consenting by reviewing patient history form and repeating the orientation (to time/place/person) status. If so found, request for recruitment into study was made, eligibility criteria were reviewed, and study procedures were explained and risks and benefits were discussed as part of the informed consent process. The consent form was then read aloud, they were asked if they understood clearly about what participation in the study would entail and if they had further queries. Any misunderstanding was clarified.

The samples were then collected. Subsequent visits were made to the hospital where the treatment progress was reviewed and an interview date was scheduled no less than 10 days since last drink. This implies that collection of blood and urine sample was done at the first instant and interviewing done at a later data when patients generally improve general condition, emotional stability, and co-operation.

In case of the rehabilitation centres, the researcher allotted Thursdays and Fridays for Richmond Fellowship Nepal, and made telephone calls to the rest of the centres to know if potential patients were available at the centre, and the centers were visited according to the availability of potential participants. The list of available patients was provided by program managers at each of the centres. This followed approaching the client by the researcher and rest of the recruitment process was same as employed for the hospital. Blood and urine samples were collected at completion of all interviews for the day in order to effectively process the sample within two hours of collection, following the guideline of the procedure received from the laboratory which would analyze the samples.

2.8.2 Interview

The interview took place in a private space to maintain confidentiality and maximize the comfort and willingness of the participant and in order to obtain honest and accurate responses. Names were not written on questionnaire but were kept on a separate folder of consent forms. All subjects were identified by an anonymous study ID and blood/urine samples were given unique number that was related to the patients' details. Names were associated with their corresponding study ID only. One interview session took no more than two hours. The interviewer read the questions to the participant taking into consideration the low literacy rates. The records of the identification were kept by the investigator with confidentiality. This was necessary for contacting the participants in course of follow up study, and in compliance with ethical review board's approval.

2.8.3 Collection of specimen, processing, storage and transport

The researcher himself collected blood and urine samples from every consenting participant. Venepuncture was defined as failed when no yield of blood more than 1 ml was obtained despite 3 attempts. The collection procedure involved the following:

1. Labeling of samples: All the test tubes and collecting vacutainers were labeled prior to collection with a water resistant unique identity sticker matched with interviewee reference number.
2. Participants were given a clean polyethylene jar for collecting mid stream urine and were instructed to transfer about 4 ml of the collection to a polypropylene tube (Sarsted, Germany. Ref. 60.550.115).
3. After applying tourniquette to either arm, antecubital fossa was prepared with rectified spirit swab. Venepuncture was done on median cubital vein with BD vacutainer 21G*1.5" (0.8*38mm) sterile needle. About 6 ml of blood was collected on a BD vacutainer (yellow cork, 8.5 ml gel tubes, BD Ref. 367953) sterile tube.
4. Sample was mixed by gently tilting the tube up-side-down for 6-8 times and transported to the biochemistry laboratory at the Tribhuvan University Teaching Hospital.
5. It was centrifuged after a time lag of 30-150 minutes at a swing-out analog centrifuge (CT6T Bench-Top Versatile Centrifuge (Licensed from Hitachi) (CT6D Export Model) at approx. 1300 g for 12 minutes.
6. Clear serum was transferred into three polypropylene tubes (Sarsted, Germany. Ref. 60.550.115), each with 1ml, using a burette and a clean burette tip. In case of

hemolysed serum, it was transferred to a fresh tube and centrifugation repeated for 5 minutes. The tubes contained no preservative.

7. The serum and urine samples were frozen at around -20 degrees at the laboratory freezer compartment that was ensured with an uninterrupted supply of power.
8. Sample was packaged with UN packaging standards and transferred through air courier in two batches using dry ice. Refilling of dry ice was done on arrival in Oslo airport and samples were delivered, in both instances, within 24 hours travel time to the laboratory at the Norwegian National Public Health Institute in Oslo.
9. The received samples were transferred to the respective laboratories, by the researcher himself, and frozen at -20 degrees or below before analyzing.

2.8.2 Specimen details:

A. Urine for analysis at Fürst laboratories: 196 (Males: 172; Females: 24)
Missing total: 8 (Refusals: 5, lost to follow: 2, drop out: 1)

B. Blood: 192 (Males: 168; Females: 24)

1. Serum for cytokine analysis: 192
2. Serum for FHI (EtG/EtS): 191
3. Serum for Fürst laboratories (GGT, CDT): 190

Missing total: 12 (8 samples missing same as for urine; 2 more refusals, 2 failed venepuncture, 1 avoided due to anxious patient). Note that several samples of collected blood were insufficient to give 1*3ml serum yield.

2.8.3 Methods of laboratory analysis:

The method of analysis for the performed test is described briefly due to the length. Details were achieved.

1. Urine EtG: machine: Olympus; specification: 03-05-Olymp; instrument: Olympus AU680; estimation by DRI Ethyl Glucuronide calibrator.

2. Urine pH: machine: Olympus, specification: 03-05 Olympus; instrument: AU680 analyzer; measured by Olympus AU680 default pH-detector, calibrator pH4 and pH9, default calibrators set at NIST pH=7.0 and pH=10 standards. Photometry.

3. Urine creatinine: machine: Olympus, specification: 03-05-Olymp; instrument: Olympus AU680, measured by: creatinine-detector calibrator, Microgenics. Photometry.

4. Serum CDT: machine: Olympus; specification: 03-05-658; measured by capillaries non-automatized. Capillary electorphoresis.
5. Serum GGT: machine: labcell; specification: 03-05- Advia 2400 and 03-05-LabCell; measured by Advia 2400; use standard: permanent systemfactor. Photometry.

2.9 Data Management

2.9.1 Data handling

Immediately following the completion of an interview, the interviewer double checked the questionnaire for completeness and consistency of answers. All collected data were checked on a weekly basis to rectify the collection method to be used on the following days. Data entry were planned to be done concurrent with data collection. But this could not happen due to lack of regular electricity supply in the field and time constraints.

All the answered questionnaires were stored safely by the researcher himself at a locked cabinet in his house. Nobody was given access to any of the data. The researcher himself brought the questionnaires to Norway as his hand carriage. The entire set of data was then stored in a fireproof cabinet at the Centre for Addiction Research (SERAF) in the university.

The biological specimens were destroyed after completing the first set of the analysis at the Fürst laboratories. The time extension for possession of the data (remaining sets of serum and urine samples stored at FHI and Inlandet hospital in Hamar, Norway) has been received and detailed in section with ethical consideration.

2.9.2 Data coding into electronic form:

All the answers in the questionnaires were coded into a single PASW version 18 data set. This comprised of 617 variables and a total of 122166 data points. A data codebook was maintained to transfer all collected details into the dataset. Whenever a data did not confer to numerical or nominal classification, a new string variable was created to enter in an understandable manner. All CIDI dichotomous replies are coded in the questionnaire as 5 (yes) 1 (no). The same was used in the code book for CIDI and other variables with dichotomous responses. Appropriate labels were given to relevant variables. All the data were entered twice and checked for consistency between the entries. A discordant set of entry was checked for correction. The questionnaire was retained until data cleaning was performed so that abnormal data could be rechecked.

Personally identifiable details were recorded in a separate spreadsheet. Then all the hard copies of the data were stored safely at fireproof lockers at SERAF.

2.9.3 Editing categories (Recoding)

The variables were checked for distribution of data and further rearranged and coded accordingly. The collected data belonged to either strings, nominal or ordinal categories or continuous categories. Some variables such as problem drinker relative were coded as nominal descriptive as 'father' or 'mother' or 'sibling' or 'second degree relative'. These were recoded into variables that dichotomized the entry into presence or absence of the phenomenon. The phenomenon of interest was recoded as 1 and absence as 0 in all cases. The CIDI entries containing responses were thus recoded for uniformity as 1(yes) and 0(no) respectively.

Age was kept a continuous variable, but newer variables were created to recode into ordinal categories of 14-24, 25-34, 35-44, 45-54, and 55-64. Yet another variable was created for younger and older age group dichotomized at the median age of 36 years. These variables were analysed/treated according to the needs. In case of depressive comorbidity, we used the dichotomous variable to observe the difference between the younger and older population. Initially, the place of origin and residence was recorded. Then these were translated into urban and rural settings by asking the participant. Finally, the variable was given 4 categories: 1. Urban origin and residence. 2. Rural origin and residence. 3. Urban origin and rural residence. 4. Rural origin and urban residence. The marital status was recoded into cohabitating marital relations or other. There was no premarital cohabitation. Family type nuclear was considered protective for most outcomes, so it was dichotomized as nuclear or non-nuclear. Several occupations were collapsed into two categories, one those having a stable source of income and the other without. Stable source of income was coded for all white collar job holders, regular staffs at businesses, and those running own business. Medium and higher income levels were collapsed together to differentiate from low income people set at the least annual pay scale at government firms (Nepalese Rupees 60,000). Education below 7 years of regular schooling and illiterates were coded as low education. Similarly, treatment centres were categorized as hospital or rehabilitation centres. Preferred beverage was classified as locally brewed (including ferment *Jand* and distilled *Raksi*) and industrially brewed spirits. Drinking frequency was dichotomized as those drinking less frequent than 2-4 times monthly or otherwise. A possible 'J' shaped relationship between

frequency of drinking and other outcomes could be overlooked by such dichotomy, so initial entries of frequency of drinking was preserved.

For all variables that required calculations, such as average HSCL, AUDIT scores, a newer variable for the calculated results were created. Calculations and categorization according to diagnostic criteria was done carefully and double checked for the correctness of the process.

2.9.4 Data analysis

All analyses for the interview data were performed using the Predictive Analytics SoftWare (PASW) Statistics version 18.0 (SPSS Inc., Chicago, IL, USA). For all the tests statistical significance were set at the 0.05 level, and two tailed significance levels reported. Data were dealt according to their type (numeric, date, strings), and measures (scale, ordinal and nominal). Whenever available, scale values were preferred for analyses. Data were first screened and cleaned according the directions of SPSS guide (110). Data were first explored to observe descriptive features in terms of mean, median, mode, standard deviation, minimum and maximum values, range, percentage, etc.). Each variables of interest were explored according to their type (i.e, continuous, categories). All missing data were carefully checked for. Symmetry of data distribution was checked with skewness test on descriptive analysis. For missing data in relation to diagnosis, we ignored missed data whenever available data met criteria for diagnosis. But if the available data that did not meet diagnostic criteria and any variables that would contribute to reaching a diagnosis was missing from the data set, we excluded the particular data from analyses. For our first paper, only one case fell into this category. Normality of continuous data distribution was tested by running Kolmogorov Smirnov statistics described in the manual (110). Extreme values lying outside the whiskers in boxplot were considered outliers in case of scores and were excluded from analyses.

Chi squared test and Fischer's exact test were utilized to investigate group difference in case of categorical variables. Most analyses presented in the table 1 of our first paper are results of chi square analyses. A two by two contingency table was created in order to observe most of the categories because it was easy to observe the distribution of our variables of interest. Student t-test and ANOVA in case of normally distributed variables and Mann-Whitney U test in case of abnormally distributed variables were performed. Dichotomous dependent variables were looked for their association with dichotomous or multiple independent variables by running binary logistic regression analyses. Explanatory variables that showed significant group differences were fitted in separate models to control for each other and the

adjusted Odds ratio were reported that spelled out the strength of the association. Further analyses were performed according to the nature of desired result in question.

Analytical process regarding the biological specimens has been detailed in a separate section. Analytical tools used in the first article have been described in the paper.

2.10 Limitations and strength of the Study

Due to the constraints of resources in terms of duration for data collection (which lasted 130 days) and human resource to interview (needing training for administration of CIDI interviews) it was not plausible to include a larger sample for study. In order to prevent misclassification of acute alcohol intoxication or withdrawal features as affective symptoms, duration of 10 days of alcohol free interval was ensured. Despite this, abstinence period of 30 days were not possible in about 32% cases, which according to several literature, is a period where such symptoms may overlap, and observed in Nepal (66).

There were other limitations of the study: This study did not intend to address the question of the causality nor the order of affliction of alcohol-use disorder and other common mental illnesses. Although a large set of data was collected, we could not record the parental depressive history. This is because we believed that it would be very non-specific record of data. As mentioned in another article, Nepalese people do not take note of things in exact dates and numbers (111). We cannot ensure the age of the participants to be their real age; we anticipate an error of up to 5 years even in the record of it. There was no verification available for the same. In the same terms, the record of drinking history in the timeline follow back may be even less accurate. Although, a number of prominent centres of alcohol treatment have been successfully engaged, these may not represent the total treatment seeking population throughout the country.

Yet another limitation of the study could be that we could not complete performing analysis so far from all the collected data meant for this Masters degree.

Strength of the study: Despite the limited human resource for data collection, we were able to collect quite a large data set of 199 individuals. Moreover, multi-centred involvement made the sample more inclusive. We do not regard underrepresentation of females in our study because virtually all females who attended treatment in Kathmandu valley during the data collection period were successfully enrolled because of a single catchment unit. This study is unique in terms of the area and population of the study. Moreover, the collected data

constitutes manifold details of explanatory and outcome variables. We believe that it will provide citable inferences regarding the dependent variables studied in the region.

The collection of blood and urine samples was strength to this study. Several findings such as concentration of alcohol metabolites will help triangulate the observations. The cytokine analysis will help substantiate our findings, and aid in our effort to check the alteration in the intricate balance between pro and anti-inflammatory cytokines.

2.11 Methodological Considerations

Results and discussion are beyond the scope of this thesis. However, relevant methodological considerations in terms of its limitation, strengths and possible sources of bias and confounding are discussed briefly.

We used a cross-sectional study design to estimate the prevalence of comorbid major depression and anxiety disorders among AUD patients. This design does not provide inferences regarding cause and effect. Neither does it provide the chronology of the disease pathology objectively. More specifically, we would not be able to ascertain whether AUD or MD was the primary pathology among co-morbidly depressed AUD patients. However, prevalence rates and associated factors for the comorbid MD could be efficiently identified and their strength of association estimated.

Methodological Limitations: Not all of the participants were free of alcohol for a minimum of 4 weeks before assessment, which might have caused erroneous recording of alcohol induced withdrawal features as anxiety and depressive symptoms. This ambitious project walked through a double-edged sword in the sense that we needed short abstinence period for accurately observing alterations in biological parameters, while at the same time, we needed adequate abstinence period for excluding short-lived alcohol induced symptoms. Secondly, the participants despite making a common cohort of treatment receiving in-house clients were more heterogeneous than similar. It is extremely difficult to generalize that the same stressor (for example, originating from urban areas) could produce effect of same nature or in the same direction (for example, depressive outcome). To add on this, we could only assume that numerous explanatory factors competed against each other in their risk to cause the same outcome.

This study could not enroll all patients with AUDs even all of the treatment seekers at three of the participating units. This made the sample neither representative nor totally inclusive.

We were left with a smaller sample size for subgroup analysis. Both type I and type II error cannot be ruled out. Another important limitation of the study was that we did not record whether the treatment sought at that particular visit was first or subsequent. Given the likely fact as suggested in a paper, Nepalese people may not keep track of time or duration. This was not only the challenge for appropriately screening duration of low mood; some of the participants were not sure about their age. We tamed the presupposition that we would be unable to determine whether problem drinking or low mood was the index case. Besides, we missed the opportunity of recording the parental depression.

Methodological strength: Our sample was inclusive and quite large given the resource constraints. We applied reasonably robust and validated assessment tools. The response rate was very high and dropout was very low. It was owing to our careful planning regarding the selection of time for specimen collection, and interviewing together with co-ordination with the participating centres. Collection of blood and urine samples was not only helpful in triangulating our findings, but could serve as a potential tool to compare with findings from elsewhere. All data collection and handling was done by a single researcher thus saving from the risk of inter-rater non-reliability. Special training for the use of CIDI instrument was taken before field visit. We used fully structured tools with diagnostic capacity and also symptom measures that would help to understand the multitude of the same disease phenomenon. There were not only selection bias common to multicenter studies but also a quick, numerous and effective. This enhanced the external validity of our findings. Moreover, we were able to recruit a majority of samples as fully inclusive from several treatment units.

Internal validity: The study had minimal attrition rates, but it was not free of bias in terms of selection and information. In order for our results to be representative to the treatment seekers of the whole country, a probability sampling method for treatment units should have been applied. Misclassification of ‘caseness’ may be more characteristics of psychiatric research in general. And patient attribution is a factor often missed to address. Level of stress as measured in HSCL-25 could be a function of stress acquired at the particular institution in course of treatment. Lack of relevant explanatory variable (often identified by ethnographic means) and small sample size may have resulted in confounding. We tried to limit this by stratification in age, testing our analytical results by controlling for different sociodemographic strata, and by running binary logistic regression analysis, as in paper I, since both age and gender are known to be notorious confounders.

Assessment validity/reliability: It relates to the appropriateness of technique for collection and testing of the samples. Though blood sample collection, serum separation, storage, and transfer was done by the researcher using the recommended preservation standards (temperature, testing time, etc), issues of standardization of the parameters in analyses was difficult to control for. The recording of drinking volume and its operationalized unit measures are more arbitrary than standard because of reporting errors and heterogeneity of ethanol concentration in locally brewed liquors. Regarding the psychometric tools, we believe that previous clinical experience in the same population helped us to interpret the self reporting of symptoms, the limitation in this process should be reckoned. Besides, there are concerns that CIDI tools may not validly pick the cultural aspects of the depressive and anxiety diagnoses among the Nepalese general population (83;112).

External validity: A robust internal validity is required in order for a study findings to be applicable in wider population. As regards paper I, the use of diagnostic tools with fully structured questionnaire to reach the diagnosis of induring major depressive episode could have balanced the under and over reporting. Alcohol dependence as a diagnosis may not be a difficult diagnosis to establish specially in the population of our study. We are claiming the validity of our findings also because positive caseness were associated with high number of positivity of individual symptoms required for diagnosis. This was elucidated by a medium concordance between HSCL-25 depressive symptoms score and MD diagnoses (Pearson's correlation coefficient= 0.34). We argue that the depressive symptoms count may not necessarily reflect the rates of MD diagnoses being made.

With this, we would like to discuss the generalizability of our findings. Kathmandu as a study site is better than nowhere else in Nepal for substance abuse research. This is because the indigenous Newar people of Kathmandu are minority, it is the largest concentration area of the whole country, and Kathmandu harbors people of all strata of sociodemographics. Kathmandu is undoubtedly a preferred site for health care. Since no publicly funded treatment is available for alcohol users, economic affordability of patients in elsewhere may be comparable to that of people in Kathmandu although threshold for treatment seeking may be different. However, our findings in no way represents the comorbidity patterns in general population levels. Generalizability to other regions should be made with caution, as both patterns of alcohol use, cultural attribution to mental illnesses, threshold for treatment seeking, and modality of treatment differs across regions.

2.12 Timetable

Department of Psychiatry at TUTH saw around 60 patients everyday from Sundays to Fridays, with a varying number of admissions per working day. There were 10 beds allocated for detoxification purposes at the de-addiction ward. Similarly, the rehabilitation centres had a capacity of between 10 and 50 clients. Patients were consecutively recruited. Ethical review took 38 days for initial review until which patient recruitment was disallowed. The data collection portion of the study lasted between 130 days (between Aug 17-Dec 28 ,2010). Data entry, data cleaning, data analysis, thesis and first article writing took another 4 months to complete. See table below for specific months of the study timeline.

Activity	Time Period
Protocol writing and research planning	April-June 2010
Training	May-June 2010
Pilot testing, ethical clearance	July-August 2010
Recruitment	August- December 2010
Data entry and data cleaning	January-February 2011
Data analysis	Febraury-April 2011
Thesis writing	April-May 2011
Thesis submission	May 2011
Paper I submission	May 2011
paper II	August-September 2011
Paper III+	Oct-Dec 2011+
Immunological analysis and Paper IV	May 2011

Table 5. Timeline of the study. Months for papers indicate the months planned for paper writing and submission. Blue shaded cells contain time plan for ongoing/planned activities which have not been completed.

2.13 Dissemination of Results

In the study protocol, we committed to distributing the results of the study in the form of thesis work. Many participants wished to receive the reports of blood and urine tests, and thus a list of the participants who wished so was prepared. The results will be sent to the respective treatment units via registered post, upon permission from the concerned ethical review board. An arrangement for contacting the participants was made in co-ordination with the host institutions. We have sent a note about this to the ethical review committees which granted approval to the study protocol. The reports will be distributed soon after such an approval for report distribution.

Owing to the richness of collected data, the analyses were done in phases and ongoing. In the first phase, correlation between our main dependent variable (major depression comorbid with an alcohol-use disorder) with demographic and clinical characteristics were examined. We attempted to explore the differences in the two social categories in regard to depressive outcome on the background of demographic and clinical explanatory variables. This made the core of our first article.

After the analysis of the data one article was written, coauthored by the supervisor, and submitted for publication in the journal '*Addiction*'. Coauthoring was done according to the Vancouver rules where the supervisor's role was inception, formulation, securing of project financing, guidance, planning statistical analyses, review, and acceptance to the final draft before submission.

The thesis was submitted to the University of Oslo and the copies are planned to be provided to collaborating institutions together with the first article after its publication. The University library of Health Sciences in Oslo will retain a copy of the same in electronic version. The report will be made available at SERAF's website and other pertinent internet pages. Publication in the local newspapers is also considered. Results of the study and its implication shall be shared with relevant governmental and non-governmental agencies.

2.13.1 Planned papers

Besides the first paper, following themes have been considered for write-up from the collected data:

1. Current psychological distress (HSCL-25) and lifetime major depression (CIDI) among AUD patients; are there correlations?

2. Descriptive study of concomitant nicotene and other substance abuse among treatment seekers of AUD in Nepal.

3. Does adverse life experiences (CIDI PTSD) predict psychiatric comorbidity among AUD patients?

4. Impairment levels of AUD patients who seek treatment- in terms of road traffic accidents, social/professional inability to deliver responsibilities, etc relating with severity and patterns of alcohol use (CIDI alcohol use module and TLFB)

5. Suicidal ideation, plans and attempts on AUD patients who sought treatment at Nepalese treatment units.

5. Usefulness of serum GGT, CDT and EtG in a resource poor setting comparing findings from elsewhere.

6. Does ethnicity modulate the intricate balance of pro-inflammatory and anti-inflammatory cytokine levels among comorbidly ill AUD inpatients? Are there differences between depressed and non-depressed AUD patients in the levels of the circulatory cytokines? How are these levels comparable to the findings from Norway?

2.14 The Researcher

The researcher is a licensed medical doctor from Nepal and has had experiences with treating the cases of depression, anxiety disorders and alcohol dependence both in inpatient and outpatient settings. He got training on the administration of WHO devised composite international diagnostic interview (see appendix and psychometrics section). He conducted all the interviews and collected the blood and urine samples. He was involved directly and solely in the data collection process, except in the laboratory analysis which took place in Norway. The processing of biological samples which took place in Nepal was also carried out by him, and is mentioned in material section.

2.15 Supervision and Collaboration

The supervision for this study was provided by Professor Dr. Jørgen G. Bramness, the research director at the Centre for Addiction Research (SERAF), Faculty of Medicine, University of Oslo. He provided supervision in the whole process from its inception to reviewing the report, in accoutring necessary funding, and forging collaboration with laboratories in Norway. His extensive knowledge and experiences in this field of research contributed substantially to assure the scientific quality and overall project management for this study. He also provided every opportunity to SPN for introducing him to scientific milieu in different arenas.

Dr. Saroj Prasad Ojha, associate Professor at the department of Psychiatry at the Institute of Medicine, Tribhuvan University, Kathmandu provided facilitation in local settings as a co-supervisor. He was responsible for negotiating with the host teaching hospital for recruitment of participants.

The participating centres provided access to their clients and a private room for data collection. The department of Biochemistry at Tribhuvan Univeristy teaching hospital granted permission for processing of blood samples and storage of blood and urine samples in a laboratory under their premises.

During data collection, Prof Helge Waal from the Centre for Addiction Research visited the field and provided his insightful advice. Training for the administration of CIDI was provided by Anne Signe Landheim at the regional competence centre for dual diagnosis in Sanderud, Norway. CIDI Questionnaires in Nepali were provided by Mark van Ommeren at WHO, Zeneva. Nepali version of AUDIT was obtained from Transcultural Psychosocial Organisation Nepal. Fürst Medical Laboratories in Oslo conducted the first series of laboratory tests. Support was received from the Toxicological laboratories at the Norwegian Public health Institute for initial collection of shipment from Nepal. Regional competence centre for double diagnosis (RKDD) in Sanderud hospital (Innlanded hospital trust, Norway) took charge of storing the biological specimen until further analyses. Financial support for SPN during the data collection and report writing period was received from the Norwegian State Educational Loan Fund. The research was funding by internal sources at the Norwegian Centre for Addiction Research (SERAF) at the University of Oslo.

List of References

Reference List

(1) Discovery Communications L. http://animal.discovery.com/ . 2011. 4-2-0011.
Ref Type: Online Source

(2) Mathers C, Fat DM, Boerma JT, World Health Organization. The global burden of disease : 2004 update. Geneva, Switzerland: World Health Organization; 2008.

(3) Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006 May 27;367(9524):1747-57.

(4) Miller NS, Gold MS. Comorbid cigarette and alcohol addiction: epidemiology and treatment. J Addict Dis 1998;17(1):55-66.

(5) Cornelius JR, Bukstein O, Salloum I, Clark D. Alcohol and psychiatric comorbidity. Recent Dev Alcohol 2003;16:361-74.

(6) Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 1990 Nov 21;264(19):2511-8.

(7) Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry 1997 Apr;54(4):313-21.

(8) Central Bureau of Statistics. Statistical year book of Nepal 2009. Kathmandu, Central Bureau of Statistics, National Planning Commission Secretariat. 2009.
Ref Type: Generic

(9) Central Intelligence Agency. The CIA World Factbook 2011. Washington, D.C. : Skyhorse Publishing; 2010.

(10) Bishop BC. Karnali under stress : livelihood strategies and seasonal rhythms in a changing Nepal Himalaya / Barry C. Bishop. Chicago, Ill. : University of Chicago; 1990.

(11) Lawoti M, Pahari A.K. The Maoist insurgency in Nepal : revolution in the twenty-first century. Lawoti M, Pahari A.K., editors. Violent conflict and change: costs and benefits of the Maoist rebellion in Nepal. 1[15], 304-326. 2010. Oxfordshire, Routledge.
Ref Type: Edited Book

(12) Dhital R, Subedi G, Gurung Y.B, Hamal P. Alcohol And Drug Use in Nepal with Reference to Children. Kathmandu: Child Workers in Nepal Concerned Centre (CWIN); 2001.

(13) Jhingan HP, Shyangwa P, Sharma A, Prasad KM, Khandelwal SK. Prevalence of alcohol dependence in a town in Nepal as assessed by the CAGE questionnaire. Addiction 2003 Mar;98(3):339-43.

(14) WHO and Ministry of Health. WHO-AIMS Report on Mental Health System in Nepal. Kathmandu, Nepal; 2006.

(15) WHO and Ministry of Health. WHO-AIMS Report on Mental Health System in Uttarkhand, India. Dehradun, Uttarkhand, India; 2006.

(16) World Health Organization. Mental health atlas 2005 / Mental Health: Evidence and Research, Department of Mental Health and Substance Abuse, World Health Organization. Geneva : World Health Organization; 2005.

(17) Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet 2009 Jun 27;373(9682):2223-33.

(18) Rehm J, Rehn N, Room R, Monteiro M, Gmel G, Jernigan D, et al. The global distribution of average volume of alcohol consumption and patterns of drinking. Eur Addict Res 2003 Oct;9(4):147-56.

(19) Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry 2004 Aug;61(8):807-16.

(20) World Health Organization. WHO Global Status Report on Alcohol 2004. http://www.who.int/substance_abuse/publications/en/nepal.pdf . 2004. 18-5-2011.
Ref Type: Online Source

(21) World Health Organization. Global Alcohol Report: Country Profile- Nepal. http://www.who.int/substance_abuse/publications/global_alcohol_report/profiles/npl.pdf . 2011. 18-5-2011.
Ref Type: Online Source

(22) Kohrt BA, Speckman RA, Kunz RD, Baldwin JL, Upadhaya N, Acharya NR, et al. Culture in psychiatric epidemiology: using ethnography and multiple mediator models to assess the relationship of caste with depression and anxiety in Nepal. Ann Hum Biol 2009 May;36(3):261-80.

(23) World Health Organization.Dept.of Mental Health and Substance Abuse. Global status report on alcohol 2004. World Health Organization; 2004.

(24) Brienza RS, Stein MD. Alcohol-use disorders in primary care: do gender-specific differences exist? J Gen Intern Med 2002 May;17(5):387-97.

(25) Manwell LB, Ignaczak M, Czabala JC. Prevalence of tobacco and alcohol-use disorders in Polish primary care settings. Eur J Public Health 2002 Jun;12(2):139-44.

(26) Shyangwa PM, Joshi D, Sherchan S, Thapa KB. Psychiatric morbidity among physically ill persons in eastern Nepal. Nepal Med Coll J 2009 Jun;11(2):118-22.

(27) World Health Organization. Mental health information systems / World Health Organization. Geneva : World Health Organization; 2005.

(28) Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994 Jan;51(1):8-19.

(29) Rickels K, Schweizer E. The clinical course and long-term management of generalized anxiety disorder. J Clin Psychopharmacol 1990 Jun;10(3 Suppl):101S-10S.

(30) Conner KR, Pinquart M, Gamble SA. Meta-analysis of depression and substance use among individuals with alcohol-use disorders. J Subst Abuse Treat 2009 Sep;37(2):127-37.

(31) Williams DR, Herman A, Stein DJ, Heeringa SG, Jackson PB, Moomal H, et al. Twelve-month mental disorders in South Africa: prevalence, service use and demographic correlates in the population-based South African Stress and Health Study. Psychol Med 2008 Feb;38(2):211-20.

(32) Levinson D, Zilber N, Lerner Y, Grinshpoon A, Levav I. Prevalence of mood and anxiety disorders in the community: results from the Israel National Health Survey. Isr J Psychiatry Relat Sci 2007;44(2):94-103.

(33) Thapa SB, Hauff E. Psychological distress among displaced persons during an armed conflict in Nepal. Soc Psychiatry Psychiatr Epidemiol 2005 Aug;40(8):672-9.

(34) Thapa SB, Van OM, Sharma B, De Jong JT, Hauff E. Psychiatric disability among tortured Bhutanese refugees in Nepal. Am J Psychiatry 2003 Nov;160(11):2032-7.

(35) Kohrt BA. Somatization and Comorbidity: A Study of Jhum-Jhum and Depression in Rural Nepal. Ethos 2005;33(1):125-47.

(36) Strandheim A, Holmen TL, Coombes L, Bentzen N. Alcohol intoxication and mental health among adolescents--a population review of 8983 young people, 13-19 years in North-Trondelag, Norway: the Young-HUNT Study. Child Adolesc Psychiatry Ment Health 2009;3(1):18.

(37) Brown SA, Schuckit MA. Changes in depression among abstinent alcoholics. J Stud Alcohol 1988 Sep;49(5):412-7.

(38) Anthenelli RM, Schuckit MA. Affective and anxiety disorders and alcohol and drug dependence: diagnosis and treatment. J Addict Dis 1993;12(3):73-87.

(39) Kushner MG, Sher KJ, Beitman BD. The relation between alcohol problems and the anxiety disorders. Am J Psychiatry 1990 Jun;147(6):685-95.

(40) Hasin DS, Grant BF. Major depression in 6050 former drinkers: association with past alcohol dependence. Arch Gen Psychiatry 2002 Sep;59(9):794-800.

(41) Schuckit MA, Tipp JE, Bergman M, Reich W, Hesselbrock VM, Smith TL. Comparison of induced and independent major depressive disorders in 2,945 alcoholics. Am J Psychiatry 1997 Jul;154(7):948-57.

(42) Schuckit MA. Alcohol and depression: a clinical perspective. Acta Psychiatr Scand Suppl 1994;377:28-32.

(43) Sullivan LE, Fiellin DA, O'Connor PG. The prevalence and impact of alcohol problems in major depression: a systematic review. Am J Med 2005 Apr;118(4):330-41.

(44) Falk DE, Yi HY, Hilton ME. Age of onset and temporal sequencing of lifetime DSM-IV alcohol-use disorders relative to comorbid mood and anxiety disorders. Drug Alcohol Depend 2008 Apr 1;94(1-3):234-45.

(45) Wang J, Patten SB. A prospective study of sex-specific effects of major depression on alcohol consumption. Can J Psychiatry 2001 Jun;46(5):422-5.

(46) Grant BF. Comorbidity between DSM-IV drug use disorders and major depression: results of a national survey of adults. J Subst Abuse 1995;7(4):481-97.

(47) Kuo PH, Gardner CO, Kendler KS, Prescott CA. The temporal relationship of the onsets of alcohol dependence and major depression: using a genetically informative study design. Psychol Med 2006 Aug;36(8):1153-62.

(48) Schuckit MA, Smith TL, Danko GP, Pierson J, Trim R, Nurnberger JI, et al. A comparison of factors associated with substance-induced versus independent depressions. J Stud Alcohol Drugs 2007 Nov;68(6):805-12.

(49) Shakya R, Situala S, Shyangwa PM. Depression during pregnancy in a tertiary care center of eastern Nepal. JNMA J Nepal Med Assoc 2008 Jul;47(171):128-31.

(50) Soyka M, Hollweg M, Naber D. [Alcohol dependence and depression. Classification, comorbidity, genetic and neurobiological aspects]. Nervenarzt 1996 Nov;67(11):896-904.

(51) Fergusson DM, Boden JM, Horwood LJ. Tests of causal links between alcohol abuse or dependence and major depression. Arch Gen Psychiatry 2009 Mar;66(3):260-6.

(52) Boden JM, Fergusson DM. Alcohol and depression. Addiction 2011 May;106(5):906-14.

(53) Flensborg-Madsen T, Mortensen EL, Knop J, Becker U, Sher L, Gronbaek M. Comorbidity and temporal ordering of alcohol-use disorders and other psychiatric disorders: results from a Danish register-based study. Compr Psychiatry 2009 Jul;50(4):307-14.

(54) Tomasson K, Vaglum P. A nationwide representative sample of treatment-seeking alcoholics: a study of psychiatric comorbidity. Acta Psychiatr Scand 1995 Nov;92(5):378-85.

(55) Pradhan SN, Adhikary SR, Sharma SC. A prospective study of comorbidity of alcohol and depression. Kathmandu Univ Med J (KUMJ) 2008 Jul;6(23):340-5.

(56) Lejoyeux M, Lehert P. Alcohol-use disorders and depression: results from individual patient data meta-analysis of the acamprosate-controlled studies. Alcohol Alcohol 2011 Jan;46(1):61-7.

(57) Lai HM, Huang QR. Comorbidity of mental disorders and alcohol- and drug-use disorders: analysis of New South Wales inpatient data. Drug Alcohol Rev 2009 May;28(3):235-42.

(58) Buydens-Branch, Branchey MH, Noumair D. Age of alcoholism onset. I. Relationship to psychopathology. Arch Gen Psychiatry 1989 Mar;46(3):225-30.

(59) Mason WA, Hawkins JD, Kosterman R, Catalano RF. Alcohol-use disorders and Depression: Protective Factors in the Development of Unique Versus Comorbid Outcomes. J Child Adolesc Subst Abuse 2010;19(4):309-23.

(60) Hesselbrock MN, Hesselbrock VM, Segal B, Schuckit MA, Bucholz K. Ethnicity and psychiatric comorbidity among alcohol-dependent persons who receive inpatient treatment: African Americans, Alaska natives, Caucasians, and Hispanics. Alcohol Clin Exp Res 2003 Aug;27(8):1368-73.

(61) Wang J, El-Guebaly N. Sociodemographic factors associated with comorbid major depressive episodes and alcohol dependence in the general population. Can J Psychiatry 2004 Jan;49(1):37-44.

(62) Cloninger CR, Bohman M, Sigvardsson S. Inheritance of alcohol abuse. Cross-fostering analysis of adopted men. Arch Gen Psychiatry 1981 Aug;38(8):861-8.

(63) Chassin L, Pitts SC, DeLucia C, Todd M. A longitudinal study of children of alcoholics: predicting young adult substance use disorders, anxiety, and depression. J Abnorm Psychol 1999 Feb;108(1):106-19.

(64) Diaz R, Gual A, Garcia M, Arnau J, Pascual F, Canuelo B, et al. Children of alcoholics in Spain: from risk to pathology. Results from the ALFIL program. Soc Psychiatry Psychiatr Epidemiol 2008 Jan;43(1):1-10.

(65) Klostermann K, Chen R, Kelley ML, Schroeder VM, Braitman AL, Mignone T. Coping Behavior and Depressive Symptoms in Adult Children of Alcoholics. Subst Use Misuse 2011 Mar 30.

(66) Khalid A, Kunwar AR, Rajbhandari KC, Sharma VD, Regmi SK. A study of prevalence and comorbidity of depression in alcohol dependence. Indian J Psychiatry 2000 Oct;42(4):434-8.

(67) Tomasson K, Vaglum P. The role of psychiatric comorbidity in the prediction of readmission for detoxification. Compr Psychiatry 1998 May;39(3):129-36.

(68) Pettinati HM. Antidepressant treatment of co-occurring depression and alcohol dependence. Biol Psychiatry 2004 Nov 15;56(10):785-92.

(69) Cornelius JR, Salloum IM, Mezzich J, Cornelius MD, Fabrega H, Jr., Ehler JG, et al. Disproportionate suicidality in patients with comorbid major depression and alcoholism. Am J Psychiatry 1995 Mar;152(3):358-64.

(70) Landheim AS, Bakken K, Vaglum P. Impact of comorbid psychiatric disorders on the outcome of substance abusers: a six year prospective follow-up in two Norwegian counties. BMC Psychiatry 2006;6:44.

(71) Sher L. Risk and protective factors for suicide in patients with alcoholism. ScientificWorldJournal 2006;6:1405-11.

(72) Schneider B, Wetterling T, Sargk D, Schneider F, Schnabel A, Maurer K, et al. Axis I disorders and personality disorders as risk factors for suicide. Eur Arch Psychiatry Clin Neurosci 2006 Feb;256(1):17-27.

(73) Vijayakumar L, Rajkumar S. Are risk factors for suicide universal? A case-control study in India. Acta Psychiatr Scand 1999 Jun;99(6):407-11.

(74) Barraclough B, Bunch J, Nelson B, Sainsbury P. A hundred cases of suicide: clinical aspects. Br J Psychiatry 1974 Oct;125(0):355-73.

(75) Cheng AT. Mental illness and suicide. A case-control study in east Taiwan. Arch Gen Psychiatry 1995 Jul;52(7):594-603.

(76) Newman SC, Bland RC. Suicide risk varies by subtype of affective disorder. Acta Psychiatr Scand 1991 Jun;83(6):420-6.

(77) Rossow I, Amundsen A. Alcohol abuse and suicide: a 40-year prospective study of Norwegian conscripts. Addiction 1995 May;90(5):685-91.

(78) Yaldizli O, Kuhl HC, Graf M, Wiesbeck GA, Wurst FM. Risk factors for suicide attempts in patients with alcohol dependence or abuse and a history of depressive symptoms: a subgroup analysis from the WHO/ISBRA study. Drug Alcohol Rev 2010 Jan;29(1):64-74.

(79) Ganz D, Sher L. Suicidal behavior in adolescents with comorbid depression and alcohol abuse. Minerva Pediatr 2009 Jun;61(3):333-47.

(80) Thong JY, Su AH, Chan YH, Chia BH. Suicide in psychiatric patients: case-control study in Singapore. Aust N Z J Psychiatry 2008 Jun;42(6):509-19.

(81) Suvedi BK, Pradhan A, Barnett S, Puri M, Rai S, Poudel P, et al. Nepal Maternal Mortality and Morbidity Study 2008/2009: Summary of Preliminary Findings. Kathmandu, Nepal: Family Health division, Department of Health Services, Ministry of Health, Government of Nepal; 2009.

(82) Mellsop GW, Menkes DB, El-Badri SM. Classification in psychiatry: Does it deliver in schizophrenia and depression? Int J Ment Health Syst 2007;1(1):7.

(83) Van Ommeren M., Sharma B., Makaju R., Thapa S, de Jong J. Limited Cultural Validity of the Composite International Diagnostic Interview's Probe Flow Chart. Transcultural Psychiatry 2000;37(1):119-30.

(84) van Ommeren M, Sharma B, Thapa S, Makaju R, Prasain D, Bhattarai R, et al. Preparing Instruments for Transcultural Research: Use of the Translation Monitoring Form with Nepali-Speaking Bhutanese Refugees. Transcultural Psychiatry 1999 Sep 1;36(3):285-301.

(85) Furr LA. On the relationship between cultural values and preferences and affective health in Nepal. Int J Soc Psychiatry 2005 Mar;51(1):71-82.

(86) Das S, Nayak P, Vasudevan D. Biochemical markers for alcohol consumption. Indian Journal of Clinical Biochemistry 2003 Jul 1;18(2):111-8.

(87) Wurst FM, Kelso E, Weinmann W, Pragst F, Yegles M, Sundstrom P, I. Measurement of direct ethanol metabolites suggests higher rate of alcohol use among pregnant women

than found with the AUDIT: a pilot study in a population-based sample of Swedish women. Am J Obstet Gynecol 2008 Apr;198(4):407-5.

(88) Sharpe PC. Biochemical detection and monitoring of alcohol abuse and abstinence. Ann Clin Biochem 2001 Nov;38(Pt 6):652-64.

(89) Hannuksela ML, Liisanantti MK, Nissinen AE, Savolainen MJ. Biochemical markers of alcoholism. Clin Chem Lab Med 2007;45(8):953-61.

(90) Hoiseth G, Bernard JP, Karinen R, Johnsen L, Helander A, Christophersen AS, et al. A pharmacokinetic study of ethyl glucuronide in blood and urine: applications to forensic toxicology. Forensic Sci Int 2007 Oct 25;172(2-3):119-24.

(91) Rosano TG, Lin J. Ethyl glucuronide excretion in humans following oral administration of and dermal exposure to ethanol. J Anal Toxicol 2008 Oct;32(8):594-600.

(92) Schleifer SJ, Keller SE, Czaja S. Major depression and immunity in alcohol-dependent persons. Brain Behav Immun 2006 Jan;20(1):80-91.

(93) Varkevisser CM, Pathmanathan I, Brownlee A. Designing and Conducting Health Systems Research Projects: Volume I. Ottawa: International Development Research Centre; 2003.

(94) Central Intelligence Agency. The World Factbook. Census 2001 & July 2011 est. 25-4-2011. 2-5-2011.
Ref Type: Online Source

(95) Thakur NC. Map of Nepal: Administrative division. http:/www.ncthakur.itgo.com/map04.htm . 2011. Thakur NC.
Ref Type: Online Source

(96) World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. http://www.wma.net [Adopted Helsinki, 1964; amended 1975, 1983, 1989, 1996, 2000, 2004 and 2008]. 2011. France, Ferney-Voltaire. 20-5-2011.
Ref Type: Online Source

(97) Brody BA. The ethics of biomedical research: an international perspective. USA: Oxford University Press; 1998.

(98) Beauchamp TaCJ. Principles of biomedical ethics. 5 ed. New York, NY: Oxford University Press; 2001.

(99) Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL). A measure of primary symptom dimensions. Mod Probl Pharmacopsychiatry 1974;7(0):79-110.

(100) Shrestha NM, Sharma B, Van OM, Regmi S, Makaju R, Komproe I, et al. Impact of torture on refugees displaced within the developing world: symptomatology among Bhutanese refugees in Nepal. JAMA 1998 Aug 5;280(5):443-8.

(101) Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol-use disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption-II. Addiction 1993 Jun;88(6):791-804.

(102) Carey KB, Carey MP, Chandra PS. Psychometric evaluation of the alcohol-use disorders identification test and short drug abuse screening test with psychiatric patients in India. J Clin Psychiatry 2003 Jul;64(7):767-74.

(103) Miller WR. Motivational enhancement therapy manual: A clinical research guide for therapists treating individuals with alcohol abuse and dependence. [2]. 1994. Rockville MD, DIANE Publishing. Project MATCH Monograph Series.
Ref Type: Serial (Book,Monograph)

(104) Sobell L, Sobell M. Timeline followback user's guide: A calendar method for assessing alcohol and drug use. 1996. Toronto, Addiction Research Foundation.
Ref Type: Catalog

(105) Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, et al. The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 1988 Dec;45(12):1069-77.

(106) World Health Organization. ICD-10 : international statistical classification of diseases and related health problems / World Health Organization. Geneva : World Health Organization; 2004.

(107) American Psychiatric Association. Diagnostic and statistical manual of mental disorders : DSM-IV. Washington, DC : American Psychiatric Association; 1994.

(108) Andrews G, Peters L. The psychometric properties of the Composite International Diagnostic Interview. Soc Psychiatry Psychiatr Epidemiol 1998 Feb;33(2):80-8.

(109) Wittchen HU. Reliability and validity studies of the WHO Composite International Diagnostic Interview (CIDI): a critical review. J Psychiatr Res 1994 Jan;28(1):57-84.

(110) Pallant JF. SPSS survival manual : a step by step guide to data analysis using SPSS version 15. Berkshire and New York. : Open University Press; 2007.

(111) Ghimire D.J., Chardoul S., Kessler R.C., Axinn W.G., Adhikari B.P. Strategies for Translating, Validating and Adapting Mental Health Measures for General Population Research in Non-Western Setting. Ann Arbor, Michigan: Institute for Social Research, University of Michigan; 2010 Jun.

(112) Tausig M, Subedi J, Broughton C, Pokimica J, Huang Y, Santangelo S. The Continued Salience of Methodological Issues for Measuring Psychiatric Disorders in International Surveys. International Journal of Mental Health and Addiction 2010 Jun 25;1-11.

APPENDICES

1. Ethical review and approval from Ethical review board, region South East Norway

UNIVERSITETET I OSLO
DET MEDISINSKE FAKULTET

KOPI

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Dato: 15.06.2010
Deres ref.:
Vår ref.: 2010/1294 (oppgis ved henvendelse)

Depresjon og alkoholbruk i Nepal 2010-2011

Vi viser til søknad mottatt til frist 29.04.2010 om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden er blitt vurdert av Regional komité for medisinsk og helsefaglig forskningsetikk i henhold til lov av 20. juni 2008 nr. 44, om medisinsk og helsefaglig forskning (helseforskningsloven) kapittel 3, med tilhørende forskrift om organisering av medisinsk og helsefaglig forskning av 1. juli 2009 nr 0955.

I følge søker finnes det ingen studier på omfanget av depresjon og alkoholmisbruk som samtidige diagnoser i en nepalsk befolkning. I denne studien vil man undersøke hvem blant de som søker behandling for alkoholproblemer som har depresjon eller angstlidelser. Studien vil videre undersøke hvor ofte slik komorbiditet øker risikoen for selvskading, og i hvilken grad pasienttilfredshet er knyttet til forekomst og alvorlighet av lidelse. Studien skal gjennomføres i Kathmandu, og er en master i internasjonal helse.

Prosjektleder: Professor Jørgen G. Bramness
Forskningsansvarlig: Professor Jørgen G. Bramness

Forskningsetisk vurdering
Komiteen har ingen forskningsetiske innvendinger til studien, men viser til søknadens punkt **5.h – tidsramme,** hvor det opplyses at resultatene vil bli brukt i en prospektiv studie planlagt umiddelbart etter dette studieprogrammet. Dette dreier seg om den påfølgende doktorgradsstudien for masterstudenten som gjennomfører prosjektet.

For ordens skyld gjør REK oppmerksom på at også doktorgradsstudien må søkes REK.

I søknaden er prosjektleder også selv oppført som forskningsansvarlig. Det forutsettes at det er SERAF som er forskningsansvarlig for denne studien, og at institusjonen er kjent med sine forpliktelser iht helseforskningslovens § 4 e).

Forskningsbiobank
Det angis i søknaden at biologisk materiale fra Nepal skal oppbevares i den eksisterende forskningsbiobanken *Kompetanseutvikling i bruk og evaluering av kartleggingsverktøy i bruk for komorbid rus og psykiatriproblematikk* (biobankmelding 1092).

Komiteen viser til den vitenskapelige protokollen som fulgte søknaden, hvor det angis at prøvene skal analyseres ved Oslo universitetssykehus, Ullevål, og deretter destrueres. Dette ble bekreftet av prosjektleder Jørgen G. Bramness på telefon fra REKs sekretariat 31.05.2010.

I Ot.prp. nr. 74 (2006-2007) heter det at prøver som ikke er ment for lagring, og som destrueres etter kort tid, ikke skal anses som forskningsbiobank. I henhold til helseforskningslovens § 4 bokstav c er det derfor ikke behov for en forskningsbiobank i prosjektet.

Informasjonsskriv og samtykkeerklæring
Det vises til følgende setning i informasjonsskrivet til deltakerne: *Reports of the study will be used in another study as well, but your identity will be confidential.* Det skal presiseres i informasjonsskrivet til deltakerne at dette dreier seg om doktorgradsarbeidet til forsker.

Ut fra dette setter komiteen følgende vilkår for prosjektet:

1. Informasjonsskriv revideres i tråd med det ovennevnte.

Vedtak:
Prosjektet godkjennes under forutsetning av at ovennevnte vilkår oppfylles.

I tillegg til vilkår som fremgår av dette vedtaket, er tillatelsen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 30.06.2011. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 30.06.2021. Opplysningene skal lagres avidentifisert, dvs. atskilt i en nøkkel- og en opplysningsfil. Prosjektet skal sende sluttmelding på eget skjema, jf. helseforskningsloven § 12, senest et halvt år etter prosjektslutt.

Komiteens avgjørelse var enstemmig.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for *Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren:*
http://www.helsedirektoratet.no/samspill/informasjonssikkerhet/norm_for_informasjonssikkerhet_i_helsesektoren_232354

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. Forvaltningslovens § 28 flg. Eventuell klage sendes til REK Sør-Øst. Klagefristen er tre uker fra mottak av dette brevet.

Med vennlig hilsen

Regional komité for medisinsk og helsefaglig forskningsetikk Sør-Øst-Norge

Arvid Heiberg (sign.)
professor dr. med.
leder

Tor Even Svanes
seniorrådgiver

Kopi: SERAF, Kirkeveien 166, 0407 Oslo

2. Ethical review and approval from Ethical review board, region South East Norway–English copy

UNIVERSITETET I OSLO

DET MEDISINSKE FAKULTET

Dr. Sudan Prasad Neupane
Seksjon for kliniske rusmiddelproblemer
Kirkeveien 166
MAR ØST, Ullevål sykehus
0407 Oslo

Regional komité for medisinsk og helsefaglig forskningsetikk Sør-Øst C (REK Sør-Øst C)
Postboks 1130 Blindern
NO-0318 Oslo

Telefon: +47 22 84 46 67

E-post: post@helseforskning.etikkom.no
Nettadresse: http://helseforskning.etikkom.no

Dato: 06.08.2010
Deres ref.:
Vår ref.: 2010/1294 (oppgis ved henvendelse)

To whom it may concern

With regards to the study *Prevalence and correlations of major depression and anxiety disorders among patients with alcohol use disorders in Nepal*

We hereby confirm that the Regional Committee for Medical and Health Research Ethics, section South-East C, Norway, has granted approval to the project *Prevalence and correlations of major depression and anxiety disorders among patients with alcohol use disorders in Nepal.* The approval was granted the 27th of May 2010.

The ethics committee system consists of seven independent regional committees, with authority to either approve or disapprove medical research studies conducted within Norway, or by Norwegian institutions.

Thus, the abovementioned study was reviewed because the research is being conducted in partial fulfillment of Masters of Philosophy degree in International Community Health at the Department of General Practice and Community Medicine, Faculty of Medicine, University of Oslo

Please do not hesitate to contact the Regional Committee for Medical and Health Research Ethics, section South-East C (REK Sør-Øst C) if further information is required.

Yours sincerely,

Arvid Heiberg MD, PhD (sign.)
Professor of Medicine,
University of Oslo

Chair, Regional Committee
for Medical and Health Research Ethics,
section South-East C

Tor Even Svanes
Senior Advisor

Regional Committee for
Medical and Health
Research Ethics, section
South-East C

3. Extension of specimen retainment period from Ethical review board, region South East Norway

UNIVERSITETET I OSLO
DET MEDISINSKE FAKULTET

Forskningsdirektør Jørgen G. Bramness
Seksjon for kliniske rusmiddelproblemer
Kirkeveien 166
MAR ØST, Ullevål sykehus
0407 Oslo

Regional komité for medisinsk og helsefaglig forskningsetikk sør-øst C (REK sør-øst C)
Postboks 1130 Blindern
NO-0318 Oslo

Telefon: 22 84 46 67

E-post: post@helseforskning.etikkom.no
Nettadresse: http://helseforskning.etikkom.no

Dato: 01.04.2011
Deres ref.:
Vår ref.: 2010/1294 (oppgis ved henvendelse)

Depresjon og alkoholbruk i Nepal 2010-2011

Vi viser til innsendt e-post for ovennevnte studie, mottatt 03.02.2011, og beklager i den sammenheng lang saksbehandling.

I e-posten gjøres det rede for at man ønsker å forlenge prosjektperioden til 31.12.2014. Det forutsettes at prosjektet ellers gjennomføres innenfor de rammer det er søkt om.

Vedtak:
Komiteen godkjenner prosjektendringen.

Tillatelsen er gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og endringsprotokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 31.12.2014. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato. Prosjektet skal sende sluttmelding på eget skjema, jf. helseforskningsloven § 12, senest et halvt år etter prosjektslutt.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for *Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren:*
http://www.helsedirektoratet.no/samspill/informasjonssikkerhet/norm_for_informasjonssikkerhet_i_helsesektoren_232354

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. Forvaltningslovens § 28 flg. Eventuell klage sendes til REK sør-øst. Klagefristen er tre uker fra mottak av dette brevet.

Med vennlig hilsen

Arvid Heiberg (sign.)
professor dr. med.
leder

Høge Holde Andersson
førstekonsulent

CIDI Composite International Diagnostic Interview

CERTIFICATION

I hereby confirm that

Sudan Prasad Neupane

has successfully participated in the CIDI training, based on the WHO-CIDI version. The trainee has also successfully completed CIDI interviews under my supervision.

Ottestad, 11. mars 2011

Anne Landheim
Associate Professor
Head of department
Centre for Addiction Issues
Innlandet Hospital Trust

Kåre Rørhus
Head of department
Associate Professor
Centre for Addiction Issues
Innlandet Hospital Trust

Nepal Health Research Council

Estd. 1991

NHRC

13 September 2010

Ref. No. 211

Dr. Sudan Prasad Neupane
Principal Investigator
Center for Addiction Research (SERAF), and
Section for international health,
University of Oslo, Norway

Ref: Approval of Research Proposal entitled **Prevalence and correlates of major depresion and anxiety disorders among patients with alcohol use disorders in Nepal**

Dear Dr. Neupane,

It is my pleasure to inform you that the above-mentioned proposal submitted on date 11 July, 2010 has been approved by NHRC Ethical Review Board on 18 August 2010 (2067-05-02).

As per NHRC rule and regulation, the investigator has to strictly follow the protocol stipulated in the proposal. Any change in objective(s), problem of statement, research question or hypothesis, methodology, implementation procedure, data management and budget that may be necessary in course of the implementation of the research proposal can only be made so and implemented after prior approval from this council. Thus, it is compulsory to submit the detail of such changes intended or desired with justification prior to actual change in the protocol.

Further, the researchers are directed to strictly abide by the National Ethical Guidelines published by NHRC during the implementation of your research proposal.

As per your research proposal, total budget is US$ 20,965 and NHRC processing fee is US$ 628.95.

If you have any questions, please contact our research section.

Thank you for your kind cooperation.

Sincerely Yours,

Dr. Shanker Pratap Singh
Member Secretary

Tel.+977-1-4254220, 4227460, Fax: +977-1-4262469, RamShah Path, P.O. Box 7626, Kathmandu, Nepal.
Website: http://www.nhrc.org.np, Email : ~~nhrc@healthnet.org.np~~ nhrc @ nhrc.org.np

Nepal Health Research Council

Estd. 1991

NHRC

Ref. No. 341

24 October 2010

Custom Declaration

Transport of Serum and Urine to Folkehelseinstituttet postboks 4404 Nydalen 0403 Oslo, Norway

To whom it may concern

In reference to the letter from PI Dr. Sudan Prasad Neupane, University of Oslo dated 21 October 2010, regarding the subject mentioned above; we hereby agree to provide a permission to transport the following shipment:

1. Human Serum (900 polypropylene tubes of size 82* 13mm, each containing 1ml of serum samples) in different batches.
2. Human Urine (300 polypropylene tubes of size 82* 13mm, each containing 4-5ml of urine samples) in different batches.

Samples shall be transported packed in dry ice. The contents of shipment are for research purpose only and safe for transport by air and are not hazardous.

Thanking you.

Yours Sincerely,

Dr. Shanker Pratap Singh
Member Secretary

Tel.+977-1-4254220, 4227460, Fax: +977-1-4262469, RamShah Path, P.O. Box 7626, Kathmandu, Nepal.
Website: http://www.nhrc.org.np, Email : ~~nhrc@healthnet.org.np~~ nhrc @ nhrc.org.np

DSM-IV Diagnostic criteria for Substance Withdrawal Delirium

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.

B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.

C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

D. There is evidence from the history, physical examination, or laboratory findings the symptoms in Criteria A and B developed during, or shortly after, a withdrawal syndrome.

Note: This diagnosis should be made instead of a diagnosis of Substance Withdrawal only when the cognitive symptoms are in excess of those usually associated with the withdrawal syndrome and when the symptoms are sufficiently severe to warrant clinical attention.

DSM-IV Diagnostic Criteria for Alcohol Abuse

1. A maladaptive pattern of alcohol abuse leading to clinically significant impairment or distress, as manifested by one or more of the following, occurring within a 12-month period:
   a) Recurrent alcohol use resulting in failure to fulfil major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions or expulsions from school; or neglect of children or household).
   b) Recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine).
   c) Recurrent alcohol-related legal problems (e.g., arrests for alcohol-related disorderly conduct).
   d) Continued alcohol use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the alcohol (e.g., arguments with spouse about consequences of intoxication or physical fights).
2. These symptoms must never have met the criteria for alcohol dependence.

DSM-IV Diagnostic Criteria for Alcohol Dependence

A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three or more of the following seven criteria, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
   a) A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
   b) Markedly diminished effect with continued use of the same amount of alcohol.
2. Withdrawal, as defined by either of the following:
   a) The characteristic withdrawal syndrome for alcohol (refer to DSM-IV for further details).
   b) Alcohol is taken to relieve or avoid withdrawal symptoms.
3. Alcohol is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or there are unsuccessful efforts to cut down or control alcohol use.

5. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol or recover from its effects.

6. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.

7. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the alcohol (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

DSM-IV Diagnostic Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
Note: Do note include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1. depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.
2. markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3. significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
4. insomnia or hypersomnia nearly every day
5. psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. fatigue or loss of energy nearly every day
7. feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Consent form

This consent is applicable to the patients attending ……..Hospital/Centre for treatment of problems related to alcohol consumption, and willing to participate in the study titled `Prevalence and correlates of major depression and anxiety disorders among patients with alcohol-use disorders in Nepa l'

PART I: Information Sheet

Introduction

I am Sudan Prasad Neupane, a Master student at University of Oslo in Norway. I am a doctor by background and doing research on alcohol use and common mental illnesses which are very common in this country. I am going to give you information and invite you to be part of this research. You do not have to decide now whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain.

Purpose of the research

Use of alcohol in our country is very common and many people have physical and mental illnesses related to this. This research is being conducted to find out how frequently are common mental illnesses associated with alcohol use and to find out the relevant socio demographic characteristics of the individuals who come to get treatment at this hospital. We want to perform blood tests to better understand this relationship.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. You may change your mind later and stop participating even if you agreed earlier.

Procedures and Protocol

Taking part in this study, we request you to answer questions I will be asking you regarding your health. We will take about 5 millilitres of blood from your arm using a syringe and a needle and we will take it only once. The blood sample will be sent to Norway for analysis and all of it will be destroyed after the laboratory tests are done. The samples collected will be used to investigate cytokine levels as well. But all your identity will be confidential. I will contact you on your address if you would like to know the results and if they are important for your treatment.

Description of the Process

During the research you will attend the interview session and give blood sample the same day. We will contact you for necessary if you agree upon. The research will last until June 2011. You might be asked to participate in follow up research in future if you choose to be contacted.

Risks/Benefits of participation

Except for your time, this study will incur no risks as such in any way. We will not ask you for any kinds of payments for the blood tests and will report the results to you if you wish to be or if they are important for your treatment. You will be offered snacks during the interview.

Reimbursements

A cash payment of Rs. 100 will be made to you for your lost work time if you are coming for interview for the research participation. You will not be given any other money or gifts to take part in this research.

Confidentiality

We will not be sharing the identity of those participating in the research. The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up. It will not be shared with or given to anyone except my University, and your clinician.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact me at the following: Sudan Prasad Neupane, Gundu 01, Bhaktpaur, Tel: 00977 1 6616857, Mobile: 00977 9841633319, email: thelonelyplanet@gmail.com

This proposal has been reviewed and approved by the national Research ethics committee in Norway and Nepal and the Research ethics committee at this hospital. These committees' task it is to make sure that research participants are protected from harm.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____ Chose to be contacted for further research Yes/No

Signature of Participant _____

Date _____ Day/month/year

If illiterate

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____

Signature of witness _____

Date _____

Day/month/year

Thumb print of participant

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done: 1. Interview

2. Blood sample collection

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

Day/month/year

(Adapted from WHO format for Informed Consent form for Clinical research, a Nepali translation for the same will be used in practice)

मन्जुरीनामा फारम

यस मन्जुरीनामा फारम त्रि.बि शिक्षण अस्पताल, काठमाडौँ /.....मा जाड रक्सि सेवनको समस्याका कारण उपचारका लागि आउनु भएको बिरामीको लागि हो जो निम्न अनुसन्धानमा शहभागी हुन यिक्षुक हुनुहुन्छ। ` alcohol-use disorders '

यस फारममा दुइ भाग छन्: क, जानकारी फारम र ख, मन्जुरीनामाको प्रमाणपत्र

भाग क. जानकारी फारम

परिचय: मेरो नाम सुदन प्रसाद न्यौपाने हो, ओस्लो बिश्योबिधायालयमा आध्ययनरत छु, पेसाले डाक्टर हु र हाल जाडरक्सीको प्रयोग र मानाशिक रोग सम्बन्धमा अनुसन्धानरत छु । यी समस्या हाम्रो देशमा निक्कै गम्भिर रुपमा रहेका छन। म तपाईलाई आबस्यक जानकारी दिदै यस अनुसन्धानमा शहभागी हुन अनुरोध गर्दछु। यस्को लागि तपाईले समय लिएर बिचार गर्न वा अरु कसै सँग परामर्श लिन सक्नुहुनेछ। कुनै कुरा बुझ्न अप्ठरो भएमा सोध्नु होला।

अनुसन्धानको उदेश्य : हाम्रो देशमा जाडरक्सी को प्रयोग ब्यप्त रहेकोछ र यस्को करणले बिभन्न शारीरिक र मानशिक समस्याहरु हुनेगरेका छन। जाडरक्सीको प्रयोग सँग मानशिक रोगको सम्बन्ध कस्तो रहेकोछ र कुन किसिमका सामाजिक र ब्यक्तिगत परिबेस सँग यि दुबै रोगको सम्बन्ध छ भन्ने कुरा पत्ता लगाउनु नै यो अनुसन्धानको प्रमुख उदेश्य रहेकोछ। उपचारको लागि आउनु भएको ब्यक्तिहरुको रक्त परिक्षण समेत गरेर यो अनुसन्धान गरिनेछ।

सोच्छिक शहभागीता: तपाईको शहभागीता पूर्ण रुपमा सोच्छिक रहनेछ। तपाइले यो अनुसन्धानमा भाग लिए वा नलिए,तपाइले यस अस्पतालबाट उपलब्ध गराईने सेवामा कुनै असर पर्नेछैन। तपाईले सहभागिता बारे निर्णय कुनै पनि बेला फिर्ता लिन सक्नु हुनेछ।

प्रक्रिया : यस अनुसन्धानमा भाग लिदा तपाईलाई व्यक्तिगत स्वास्थ्य सम्बन्धी प्रश्नहरु सोधिनेछ. केवल एक पटक तपैको पाखुरा बाट ५ मि.लि. रगत र ३ मिलिलिटर पिसाप जाचको लागि नर्बे पठाईनेछ। र उल्लेखित जाच सकेपछि उक्त रगत पूर्ण रुपले नस्ट गरिनेछ। एस पछि मैले गर्ने आध्ययनमा पनि उक्त रेपोटको प्रयोग गरिनेछ। तर तपाईको परिचय गोप्य रखिनेछ। यदि तपाईलाई यिच्छा छ भने र उपचारको दृष्टिले महत्तोपूर्ण छ भने रिपोर्ट सहित सम्पर्क गरिनेछ।

प्रक्रिया विवरण : यस सन्दर्भमा तपाईको अन्तरबार्ता र रक्त/ पिसाप संकलन एकै दिन गरिनेछ। आवश्यक भेटघाटका लागि तपाईको अनुमतिमा सम्पर्क गरिनेछ। यस अध्ययन ई.सं २०११ को जुन महिना सम्म जारि रहनेछ। यस पछिको अध्ययनमा यिक्षुक व्यक्तिलाई सम्पर्क गर्न सकिनेछ ।

सहभागिताका फाइदा/बेफाइदा: तपाईको समय बाहेक यस अध्ययनका कारण कुनै किसिमको बेफाइदा हुनेछैन। केहि परिक्षणका रिपोर्टहरु तपाईको उपचारको दृष्टिले फाइदाजनक हुनेछन। तपाइलाई रक्त परिक्षणका लागि भनेर वा अन्य कुनै कारणले कुनै किसिमको सुल्क लिईनेछैन। अन्तरबार्ताको क्रममा सामान्य नास्ताको व्यवस्था गरिनेछ। पुराना घटनाक्रमहरुको स्मरणले तपाईलाई केहि अप्ठ्यारो महशुस हुन सक्छ। त्यस अबस्थामा तपाईलाई सहज अनुभब गर्न सघाईनेछ। कृपया आफ्ना समस्या वा जिज्ञाशा भएमा अन्तरबार्ताको अन्तिममा सोध्नुहोला।

खर्चको व्यवस्था: यदि अन्तर्बार्ताको निम्ति घरबाट आउनुभाको छ भने तपैको अन्तर्बार्ताको निम्ति खर्चिनु भएको समयका लागि रू. १०० र गाडी भाडाको लागि अधिकतम रु. २५० खर्च उपलभ्द गरिनेछ। अन्य कुनै किसिमको सुबिधा उपलब्ध गरिनेछैन।

गोपनियता: यस अध्ययनका सहभागीको परिचय खुलाशा गरिनेछैन। सम्पूर्ण विवरण गोपनिय ढंगले राखिनेछ। तपाईको व्यक्तिगत विवरण र अन्तरबार्ता विवरण र रक्त/ पिसाप परीक्षणको रिपोर्ट एक संकेत नंबर बाट सम्बन्धित गराईनेछ। सो संकेत नं को सम्बन्ध मलाई मात्र थाह हुनेछ। उपोरोक्त विवरण ओस्लो बिस्वोविद्यालय, वा तपाईको उपचारमा संलग्न चिकित्शक संग मात्र आदानप्रदान गरिनेछ।

प्रतिवेदन आदानप्रदान : यस अध्ययन बाट प्राप्त हुने नतिजा तपाईको चिकित्सक मार्फत अस्पतालमा रेकर्ड गरिईने छ। भबिश्यमा तपाईको उपचारमा उक्त नतिजाको महत्व बारे तपाईको उपचारमा संलग्न चिकित्शक संग छलफल गरिनेछ। व्यक्तिगत विवरण बाहेकका बैज्ञानिक प्रयोजनले महत्तोपूर्ण विवरण विभिन्न माध्यमबाट आदानप्रदान गरिनेछ। यस बाट यिक्षुक व्यक्ति वा समुहले यस अनुसन्धानको अध्ययन गर्न सक्नेछन।

नकार्न सकिने तपाईको अधिकार : तपाईलाई एस अध्ययनमा यिच्छा नभएको खण्डमा सहभागी नहुने पूर्ण अधिकार छ। तपाईको यस निर्णयले अस्पतालबाट उपलब्ध गराईने कुनै पनि सुबिधामा कुनै किसिमको असर पर्नेछैन। तपाईको यस्तो निर्णयले कुनै अवस्थामा पनि असर पार्नेछैन।

सम्पर्क ठेगाना :

तपाईलाई कुनै किसिमको जिज्ञाशा भएमा अहिले वा पछि पनि सोध्न सक्नुहुनेछ। पछि सम्पर्कको लागि निम्न ठेगाना प्रयोग गर्न सक्नु हुनेछ।

सुदन प्रसाद न्यौपाने, पो बक्स १३१२३ काठमाडौं .फोन नं. ९८४१६३३३१९

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नोट: यस अनुसन्धान नर्बेको राष्ट्रिय इथिकल बोर्ड अन्तर्गतको कमिटी र नेपाल स्वास्थ्य अनुसन्धान परिषद बाट स्वीकृती प्राप्त छ। अब तपाईले यस अनुसन्धान सम्बन्धि कुनै जिज्ञाशा राख्न सक्नुहुन्छ। कुनै प्रश्न वा जिज्ञाशा छ?

भाग २. मन्जुरीनामाको प्रमाणपत्र

मैले उपरोक्त जानकारी पाए, वा सो जानकारी मेरो लागि पढेर सुनाइएको छ। यसको बारेको थप जानकारी लिने अवसर उपलब्ध गरियो र जिज्ञाशाको सन्तोषजनक जबाफ पाएँ। म सोच्छिक रुपमा यस अध्ययनमा सहभागी हुन मन्जुर छु।

थप अध्ययनका लागि सम्पर्क गरिन चाहन्छु/चाहदिन (ठीक लगाउने)

सहभागीको पुरा नाम, थर :

सहभागीको ठेगाना:

फोन नं :

सहभागीको हस्ताक्षर :

मिति:

सहभागीको औलाको लाप्चे छाप

निरक्षरको लागि

मैले नीज सहभागीलाई आवश्यक जानकारी दिने मन्जुरीनामा पढिएको सुने र नीज सहभागी लाई प्रश्न गर्न मौका दिएको समेत हेरे। यस अध्ययनको लागि साक्षी बस्दै छु र शहभागीले पूर्णरुपले सोच्छिक मन्जुरीनामा दिएको पक्का गर्दछु।

साक्षीको पुरा नाम, थर :

साक्षीको हस्ताक्षर :

मिति :

अनुसन्धानकर्ता वा मन्जुरीनामा भराउने व्यक्तिको बक्तब्य:

मैले पूर्णरूपमा जानकारी फारम पढेर सहभागीलाई सुनाए अनि मेरो क्षमताले भएसम्म उहालाई निम्न कुराहरु गरिने बुझाए।

क. अन्तरबार्ता

ख. रगत संकलन

अनुसन्धानको सम्बन्धमा सहभागीलाई प्रश्न गर्ने मौका दिईएको र मेरो क्षमताले भ्याएसम्म बुझ्ने गरि जबाफ दिएको कुरा प्रमाणित गर्न चाहन्छु। नीजलाई सोका लागि कुनै किसिम को दबाब दिएको छैन र मन्जुरीनामा पूर्ण रूपले स्वोतन्त्र र सोच्छिक भएको प्रमाणित गर्दछु।

यो मन्जुरीनामको एक प्रति सहभागीलाई उपलब्ध गराईएको छ.

अनुसन्धानकर्ता वा मन्जुरीनामा भराउने व्यक्तिको नाम, थर:

अनुसन्धानकर्ता वा मन्जुरीनामा भराउने व्यक्तिको हस्ताक्षर:

मिति:

(बिश्वो स्वास्थ्य संगठनको अनुसन्धानका लागि प्रयोग गरिने फारमको आधारमा नेपालीमा अनुवादित प्रति)

SECTION A: Demography

INTERVIEWER'S NAME _____ INT CODE ___/___/___

ID CODE ___/___/___/___/___/___/___ LANGUAGE OF INTERVIEW____
TIME BEGAN ____ TIME ENDED___ DATE DAY___/___MO___/___YR___/___

A1. SEX AS OBSERVED (cross).
MALE 1.....
FEMALE 2.....

A2. How old are you?
AGE ____ STRATIFY: 14-22____22^{+}-35___35^{+}-55___56^{+}__
(ASK DATE OF BIRTH WHERE APPROPRIATE) DAY___/___ MO___/___ YR___/___

A3. Where have you been living in the past 5 yrs?
_____Your place of origin?_____(Urban1/Rural 2)_____

A4. What ethnic background are do you belong to? (Don't ask when obvious)
Brahmin 1__Chhetri 2___Newar 3__Tamang 4__Rai/Limbu/Gurung 5__Sherpa 6__Magar 8__Madhesi9__
STRATIFY: TAGADHARI A1_____/MATWALI A2 _____

A5. Are you presently married, or are you widowed, separated, divorced, or have you never been married?
Never married.....1
Married and/or cohabiting.....2
Divorced or living separately.....3
Widowed or other…..4

A6. How many children have you had, not counting who are yours by adoption or who were born dead?
__

A7. What is your current occupation?

Unemployed 1__gharelu industry 2__ farmer 3__ service (private or government firms)4__own business 5__ (Mention if others)___

A8. How many years of schooling have you completed?

None 1__, some school (up to 7 years or attended adult education)2__Secondary (8-12years)3__

University 4__

Mention if still at school_____

A9. Do you usually speak Nepali at home?
Yes__ No__ . If No, Mother tongue_____

A10. How do you find yourself socially supported morally and logistically when you are in need of some kind?
None 1___
Some 2___
Adequate 3___
A11. Significant other (Yes/No), particular (relation)_____

Patient Satisfaction And General Health Questionnaire

1. In general, how satisfied are you with the treatment you have been offered which you sought for your drinking problem ?

Very dissatisfied……1
Dissatisfied……2
Neither satisfied nor dissatisfied…..3
Satisfied……4
Very satisfied……5

2. Have you ever suffered from any kind of illness for longer than three months? (If yes, mention)

Yes/ No Particular:

3. Have you ever had any sorts of surgeries under anesthesia? (If yes, mention)

Yes/ No Particular:

4. Are you currently on any medications? (If yes, mention)

Yes/ No Particular:

5. Do you smoke cigarettes? Chew tobacco or smoke hukka? (If yes, mention) If **No**, skip

Yes/ No Particular(type, quantity and frequency/day/duration):

6. Did you use to smoke cigarettes? Chew tobacco or smoke hukka? (If yes, mention)

Yes/ No Particular(type, quantity and frequency/day/duration):

7. Problem drinking in family: (Yes/No) (relation)_____

7. What is your ambition in life? (Record verbatim)

……
……

INTERVIEWER RATING:.

X1. DID R ANSWER **ALL** APPLICABLE QUESTIONS?

X2 DID R REFUSE TO ANSWER **ANY** QUESTION(S)?

A. HOW MANY QUESTIONS DID R REFUSE? ___/___/___

B. WHICH QUESTIONS DID R REFUSE?

X3 DID R UNDERSTAND ALL QUESTION(S)?

A. WHICH QUESTIONS DIDN'T R UNDERSTAND?

X4 IS R A MEMBER OF AN ETHNIC MINORITY?

A. IS R'S ETHNIC GROUP OF HIGH OR LOW STATUS?

X5 WAS THE INTERVIEW A BREAK-OFF?

A. WHAT WAS THE REASON FOR THE BREAK-OFF?

B. WHAT WAS THE LAST QUESTION ANSWERED BY R?

X6 WHAT WAS R'S RESPONSE TO POSSIBLE FUTURE INTERVIEW?

EAGER .....1 RECEPTIVE.....2 NO REACTION.....3 RELUCTANT.....4 REFUSED.....5

X7 WAS THE INTERVIEW GIVEN IN MORE THAN ONE SESSION?

A. AFTER HOW LONG WAS THE INTERVIEW INTERRUPTED? HRS _____ MINS _____/_____

B. AFTER WHAT QUESTION? Q. ___/___/___

X9 INTERVIEWER'S DESCRIPTION OF RESPONDENT AND INTERVIEW:

The Hopkins Symptom Checklist 25[3]

	I. Questions for Anxiety	Not at all (हुदै भएन)	A little (कहिलेकाँही भो)	Quite a bit (अकसर भो)	Extremely (एकदमै धेरै भो)
१.	(Suddenly scared for no reason) विनाकारण एक्कासी डर लाग्ने भयो कि भएन?कत्तिको भयो ?	1	2	3	4
२.	(Feeling fearful) त्यत्तिकै आफ्नो मन डराएको सोचाइ आयो कि आएन ? कत्तिको आयो ?	1	2	3	4
३.	(Faintness, dizziness or weakness) चक्कर लाग्ने, भाउन्न हुने वा कमजोरी महसुस हुने भयो कि भएन ? कत्तिको भयो ?	1	2	3	4
४.	(Nervousness of shakiness inside) मन आत्तिने,नर्भस हुने भयो कि भएन ? कत्तिको भयो ?	1	2	3	4
५.	(Heart pounding or racing) मुटु हल्लिने (छिटो छिटो ढुकढुक गर्ने) समस्या भयो कि भएन ? कत्तिको भयो ?	1	2	3	4
६.	(Trembling) हातखुट्टा वा पुरै शरीर काम्ने भयो कि भएन ? कत्तिको भयो ?	1	2	3	4
७.	(Feeling tense of keyed up) टेन्स् वा तनावग्रस्त भएको अनुभव भयो कि भएन ? कत्तिको भयो ?	1	2	3	4
८.	(Headaches) टाउको दुख्यो कि दुखेन? कत्तिको दुख्यो ?	1	2	3	4
९.	(Spells of terror or panic) डरले एकदमै र झ्वाट्टै आत्तिने भयो कि भएन ? कत्तिको भयो ?	1	2	3	4
१०.	(Feeling restless and can't sit still) चुपचाप लागेर शान्तसंग बस्न नसक्ने गरी छट्पटी भयो कि भएन ? कत्तिको भयो ?	1	2	3	4

[3] **Note: Nepali script readable in Himchuli font. Please refer to the hard copy for instant readability.**

The Hopkins Symptom Checklist 25[4]

	II. Questions for Depression	Not at all (हुदै भएन)	A little (कहिलेकाँही भो)	Quite a bit (अकसर भो)	Extremely (एकदमै धेरै भो)
१.	(Feeling low in energy, slowed down) कमजोरी भएको वा शक्ति नभएको जस्तो अनुभव भयो कि भएन ?यस्तो कत्तिको भयो ?	1	2	3	4
२.	(Blaming yourself for things) जे काम बिग्रे पनि आफ्नै गल्तिले बिग्रेको भन्ठान्नु भयो कि भएन ? यस्तो कत्तिको भयो ?	1	2	3	4
३.	(Crying easily) जतिबेला पनि सजिलै सित रुन मन लाग्ने भयो कि भएन ? यस्तो कत्तिको भयो ?	1	2	3	4
४.	(Loss of sexual interest or pleasure) श्रीमान्/श्रीमतीसँग यौन सम्पर्कमा रमाइलो नहुने भयो कि भएन ? यस्तो कत्तिको भयो ?	1	2	3	4
५.	(Poor appetite) केही खान मन नलाग्ने भयो कि भएन ? यस्तो कत्तिको भयो ?	1	2	3	4
६.	(Difficulty falling asleep, staying asleep) निदाउन गाह्रो हुने वा निन्द्रामा बिउझिरहने भयो कि भएन ? यस्तो कत्तिको भयो ?	1	2	3	4
७.	(Feeling helpless about the future) अब म केही पनि गर्न सक्दिन, अब मेरो हालत के हुने होला भन्ने सोचाइ आयो कि आएन? यस्तो सोचाइ कत्तिको आयो?	1	2	3	4
८.	(Feeling blue) मन उदास वा खिन्न हुने भयो कि भएन ? यस्तो कत्तिको भयो ?	1	2	3	4
९.	(Feeling lonely) आफ्नो भन्ने कोही छैन भनी एक्लोपनको महसुस गर्नुभयो कि भएन ? यस्तो महसुस कत्तिको गर्नुभयो ?	1	2	3	4
१०.	(Thoughts of ending your life) आत्महत्या गर्ने, मरुँ मरुँ लाग्ने सोचाइ आयो कि आएन ? यस्तो सोचाइ कत्तिको आयो ?	1	2	3	4
११.	(Feeling of being trapped or caught) केही कुरामा आफु फसेको जस्तो सोचाइ आयो कि आएन ? यस्तो सोचाइ कत्तिको आयो ?	1	2	3	4
१२.	(Worrying too much about things) जुनसुकै कामकुराको वारेमा पनि ज्यादा सुर्ता लाग्ने भयो कि भएन ? यस्तो कत्तिको भयो ?	1	2	3	4
१३.	(Feeling no interest in things) काम कुरा केही गर्नै मन नलाग्ने भयो कि भएन यस्तो कत्तिको भयो ?	1	2	3	4
१४.	(Feeling everything is an effort) कुनै पनि कामकाज गदा मिहिनेत गर्नु परेको वा गाह्रो भएको अनुभव भयो कि भएन ? यस्तो कत्तिको भयो ?	1	2	3	4
१५.	(Feeling of worthlessness) आफूले आफैंलाई काम नलाग्ने, बेकारको मान्छे ठान्नुभयो कि भएन ? यस्तो कत्तिको ठान्नुभयो?	1	2	3	4

[4] **Note: Nepali script readable in Himchuli font. Please refer to the hard copy for instant readability.**

THE AUDIT QUESTIONNAIRE

Circle the number that comes closest to the patient's answer.

1. How often do you have a drink containing alcohol?
   (0) NEVER (1) MONTHLY OR LESS (2) TWO TO FOUR TIMES A MONTH (3) TWO TO THREE TIMES A WEEK (4) FOUR OR MORE TIMES A WEEK

2. *How many drinks containing alcohol do you have on a typical day when you are drinking? [CODE NUMBER OF STANDARD DRINKS]
   (0) 1 OR 2 (1) 3 OR 4 (2) 5 OR 6 (3) 7 TO 9 (4) 10 OR MORE

3. How often do you have six or more drinks on one occasion?
   (0) NEVER (1) LESS THAN MONTHLY (2) MONTHLY (3) WEEKLY (4) DAILY OR ALMOST DAILY

4. How often during the last year have you found that you were not able to stop drinking once you had started?
   (0) NEVER (1) LESS THAN MONTHLY (2) MONTHLY (3) WEEKLY (4) DAILY OR ALMOST DAILY

5. How often during the last year have you failed to do what was normally expected from you because of drinking?
   (0) NEVER (1) LESS THAN MONTHLY (2) MONTHLY (3) WEEKLY (4) DAILY OR ALMOST DAILY

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
   (0) NEVER (1) LESS THAN MONTHLY (2) MONTHLY (3) WEEKLY (4) DAILY OR ALMOST DAILY

7. How often during the last year have you had a feeling of guilt or remorse after drinking?
   (0) NEVER (1) LESS THAN MONTHLY (2) MONTHLY (3) WEEKLY (4) DAILY OR ALMOST DAILY

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
   (0) NEVER (1) LESS THAN MONTHLY (2) MONTHLY (3) WEEKLY (4) DAILY OR ALMOST DAILY

9. Have you or someone else been injured as a result of your drinking?
   (0) NO (2) YES, BUT NOT IN THE LAST YEAR (4) YES, DURING THE LAST YEAR

10. Has a relative or friend or a doctor or other health worker been concerned about your drinking or suggested you cut down?
    (0) NO (2) YES, BUT NOT IN THE LAST YEAR (4) YES, DURING THE LAST YEAR

* In determining the response categories, it has been assumed that one "drink" contains 10 g alcohol. In countries where the alcohol content of a standard drink differs by more than 25% from 10 g, the response category should be modified accordingly.

Record sum of individual item scores here _____.

Timeline Followback sample calendar (30 days)[5]

भाद्र २०६७			नेपाल सम्बत् ११३०			August-September 2010
आइत Sun	सोम Mon	मंगल Tue	वुध Wed	विही Thu	शुक्र Fri	शनि Sat
		१ अष्टमी 17	२ नवमी 18	३ दशमी 19	पुत्रदा एकादशी ४ एकादशी 20	५ द्वादशी 21
६ त्रयोदशी 22	७ चतुर्दशी 23	ऋषितर्पणी रक्षाबन्धन ८ पूर्णिमा 24	गाईजात्रा ९ प्रतिपदा 25	१० द्वितीया 26	११ त्रितीया 27	१२ चतुर्थी 28
१३ पञ्चमी 29	१४ षष्ठी 30	१५ षष्ठी 31	श्रीकृष्ण जन्माष्टमी व्रत १६ सप्तमी 1	१७ नवमी 2	१८ दशमी 3	अजा एकादशी १९ एकादशी 4
२० द्वादशी 5	२१ त्रयोदशी 6	जुगः चन्द्रे पूजा (पञ्च दान) २२ चतुर्दशी 7	बाबुको मुख हेर्ने दिन (कुशे औंशी) २३ औंसी 8	२४ प्रतिपदा 9	२५ द्वितीया 10	हरितालिका (तीज) २६ त्रितीया 11
ऋषिपञ्चमी व्रत २७ चतुर्थी 12	२८ पञ्चमी 13	२९ सप्तमी 14	३० अष्टमी 15	३१ नवमी 16		

[5] Note that this is a sample monthly calendar provided for reference to the participant. Responses were recorded in a plain dated sheet with unit and type of beverage on each date.

PAPER I [6]

[6] Please note that the structure and length of the article is based on the requirement of research reports for submission to the journal *Addiction*

Comorbidity of major depression in alcohol-use disorders within an ambivalent society: the case of Nepal.

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Running head: AUD-MD Comorbidity in Nepal

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0. Abstract

Introduction Nepal is an ambivalent society in terms of alcohol use: alcohol consumption is frowned upon among traditionally ruling upper caste people whereas its use is socially accepted among certain lower caste people. We hypothesized that presence of social taboo leads to higher rates of depression among consumers of alcohol and that the explanations of comorbid depression across the two strata could be different. **Aims** 1) To investigate if belonging to the tabooed social stratum led to higher rates of concomitant major depression. 2) To correlate sociodemographic and clinical factors with the presence of major depression in the two social strata. **Methods** A cross-sectional survey was carried out among consecutively admitted 188 Alcohol-use disorder (AUD) patients in multiple residential alcohol treatment units in Kathmandu during the period July- December, 2010. We recorded socio-demographic data and administered the alcohol use and depression modules of WHO Composite International Diagnostic Interview (CIDI) 2.1, and the Alcohol-use disorder Identification Test (AUDIT). **Results** Depressed AUD patients compared to non-depressed AUD patients had significantly more severe alcohol problems and were less likely to be cohabitating with a partner. Lifetime and 12-month prevalence of major depressive episodes among the alcohol abuser/dependent patients were found to be 45% and 36% respectively, with marginally higher rates of major depression in the non-tabooed group. Lacking a stable employment, having experienced alcohol-induced blackout, and longer abstention were positively associated with major depression in the non-tabooed group. In case of the tabooed group, parental problem drinking appeared to be the single most important independent correlate (OR=7.7, 95% CI= 2.6-22.3) of comorbid MD. **Conclusions** Major depression is common among patients with alcohol-use disorders in Nepal. Among treatment seekers, social taboo on alcohol use seems to have insignificant effect on rates of comorbidity. However, lack of stable source of income and alcohol problem severity in case of the non-tabooed class and familial predisposition in case of the tabooed class may indicate potential risk factors for depressive comorbidity.

Keywords: Nepal, alcohol, depression, comorbidity, taboo.

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1. Introduction

Unipolar depressive disorders and alcohol-use disorders (AUDs) constitute the leading causes of years lost due to disability worldwide, contributing 6% to the global burden of diseases (1). Low- and middle-income countries bear a majority of this burden (2-4). Meanwhile, a number of epidemiological surveys (5-8) and clinical studies (9-11) have quite well substantiated the frequent comorbidity between AUDs, particularly alcohol dependence, and major depression (MD). Approximately one-third of the patients with AUDs, suffer from concurrent MD (12), and more depressed than non-depressed AUD patients seek treatment (13). Co-occurring depression among AUD patients not only impairs neuropsychological functioning (14) but also predicts relapse to alcohol use (15) and increased risk for suicidal behaviour (16).

Several sociodemographic and clinical traits may play a moderating role in the comorbidity between AUD and MD. Alcohol abuse and dependence are more prevalent among males. In tandem with gender paradigm of MD in population level, depressive symptoms following AUD is more common among females (17-19), but neither depression nor problem drinking is a province of either gender alone. Older age (17), early onset of alcohol abuse (20;21), white race (17;22), and low socioeconomic status (23) are often implicated as risk factors for major depression among patients with AUDs. Furthermore, a number of randomized controlled trials involving cohorts receiving acamprosate treatment identified younger age, unemployment, single living and episodic drinking as vignettes of depressed alcohol-dependent patients (24). Another notion attributes depressive comorbidity to the pattern of alcohol consumption and severity of problems caused by harmful drinking. Following Cloninger's proposed typologies of alcoholism (25), a number of studies have investigated the children of problem drinkers suggesting that parental problem drinking relates both to AUDs and depressive mood in the off springs (26-28). The applicability of these findings

need to be corroborated in non-Western settings. A meta-analysis of findings from 74 studies, mostly from clinical venues, concluded that AUD patients belonging to racial minority generally report lower levels of depression than do their Caucasian counterparts (17). The generalizability of these findings are, however, limited because the disparity in rates of comorbidity could be an artifact produced by differential treatment seeking in natives and non-native people (29). Most of the literature by virtue of their research settings list Asian population as a minority group, or often as 'others' thus leading to little inferable details.

Nepal is a low-income level secular republic lying between India and China. Over 80% of its 29 million inhabitants follow Hinduism (30), having a multifaceted construct of caste system. Caste determines an individual's behaviour, obligations and expectations in the society (31), also those relating to alcohol usage. An archaic civil code in 1854 classified the entire population into two distinct groups: the 'Tagadhari' and the 'Matwali' community. The higher castes, viz. Brahmins (the priests and teachers), Kshetriyas and Thakuris (the warriors and rulers) constitute the Tagadharis who wear holy cord around their body and among whom alcohol use is normatively restricted. On the contrary, consumption of alcoholic drinks is banal among the Baishyas (traders, farmers, artisans) and lower castes (labourers) that constitute the Matwalis (literally meaning alcohol users). This largely ambivalent society has grown to incorporate oriental drinking culture backed by domestic brewing and widespread consumption of industrially brewed liquors. Both depression and alcohol dependence are associated with considerable shame and stigma in Nepal; alcohol use is specifically tabooed among the Tagadharis. Compared with low caste people, high caste people show higher abstinence rates (85% vs. 40%, 12-month) (32), but significantly lower depression rates (33). Albeit limited, studies indicate that both AUDs and MD are highly prevalent among Nepalese populations (33-36).

Two studies on Nepalese AUD patients varied in their results between 17% and 94% on comorbid MD (37;38), thus necessitating further investigation. Of particular concern is the alarmingly high proportion of younger population whose drinking career starts even before adolescence (32). Few hospitals run detoxification services to substance dependent individuals and an increasing number of 12-step based rehabilitation centres are operating in towns. Too little is known about the patient characteristics and affective comorbidity among treatment receivers at these centres. Enduring social taboo on alcohol use germane to most oriental cultures may have bearing in the depressive psychopathology. Conversely, such taboo may alter the threshold of self medicating behavior. In the present study of treatment receiving alcohol-use disorders patients, we aimed to estimate the prevalence of major depression and investigate if belonging to the tabooed stratum led to increased rates of major depression and whether different factors were related to the presence of major depression in the two social strata.

2. Materials and methods

2.1 Sample and settings

A total of 221 individuals 14 years of age and above who were consecutively admitted to the detoxification unit of Tribhuvan University Teaching Hospital and seven conveniently selected drug/alcohol rehabilitation units in Kathmandu and Lalitpur districts of Nepal were considered for participation in this study. Exclusion criteria included: (1) current intoxication or ongoing complicated withdrawal; (2) disorientation; and (3) ongoing psychotic symptoms. In all, 11 refused to participate, five dropped out, and six were excluded. Another 11 (5.5%) of the interviewed individuals did not meet the DSM-IV diagnostic criteria either of alcohol abuse or alcohol dependence giving a sample of 188 (85%) patients with an AUD who hailed from 44 out of 75 districts of Nepal. Interviews were conducted during August- December 2010.

A team of psychiatrists and clinical psychologists provided benzodiazepine based detoxification, followed by counseling services during a two-week long stay at the hospital. The remaining seven institutions were non-governmental rehabilitation units and comprised of 12-step based therapeutic communities. Choice of centre was voluntary and treatment was based on out-of-pocket expenditure. Patients developing delirium tremens more commonly presented to the hospital.

2.2 Instruments and Assessment

Participants completed questionnaires that assessed characteristics including gender, age, urbanity of origin and current residence, marital status (never married, married and cohabitating, divorced or living separately or widowed), family type (nuclear, joint or

extended), education (illiterate, seven years or lower, 8-12 years, or higher), employment status (unemployed, student, farmer/domestic work, job holder, or driver/labourer/foreign employment) and personal annual income levels (below 60,000, 60,000-100,000, above 100,000 Nepalese Rupees). Participants self-identified belonging to either Tagadhari or Matwali community, and reported their perceived adequacy of social support system. They were also asked if any of their parents were known to have had problem drinking in their lifetimes.

The main variables were alcohol abuse, alcohol dependence, and major depressive episodes (as dependent variable), all of which were assessed by using the World Health Organization Composite International Diagnostic Interview (CIDI) (39). CIDI is a fully structured comprehensive interview compatible with the definitions and criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (40). The depression and alcohol use modules used in this study have shown acceptable reliability and validity in a number of studies across a wide range of cultures (41). Nepali version of CIDI (Version 2.1) used in this study was previously translated by following standard procedures and administered to Nepali speakers (42). Regarding the depression module, both lifetime and 12 month responses were recorded. In order to limit possible underreporting, screening symptoms of low mood and anhedonia were inquired first without a time string, unlike in the official CIDI which requires that the individual have experienced either of these two symptoms more often than not for at least two consecutive weeks. MD is referred here to 12-month major depressive episodes as measured by CIDI unless otherwise specified.

We also used the World Health Organization Alcohol-use disorder Identification Test (AUDIT) which screens an individual with three questions about hazardous alcohol use, three about dependence symptoms and four about harmful alcohol use (43). This tool has enjoyed widespread use in clinical and research settings, including demonstrated psychometric

properties in a similar setup (44). The two variables regarding consumption of alcoholic beverage as the first thing in the morning (eye-opener) and periods of anterograde amnesia (alcohol-induced blackouts) as lifetime experiences were constructed from responses to AUDIT.

Despite the possibility of a large variation in the concentration of locally brewed liquors, one small bar served glass (roughly 0.2L) of *Rakshi* (distilled local drink) which is a common volume measure in Nepal, was considered 2 standard units of alcohol. Similarly, 1 *mana* (approximately 0.55L) of *Jand* (domestically fermented drink) was considered equivalent to 3 units.

2.3 Procedure and ethics

Owing to high rates of illiteracy, all questionnaires were paper-and-pencil versions in Nepali language and administered by the first author, who also received training to use CIDI. In order to limit over-reporting of withdrawal features as axis I symptoms the questionnaires were administered no less than 10 days since last drink. All potential candidates available during the study period were successfully approached in all but three of the centres in which case available patients were recruited in descending order of their recency of last alcohol intake. A written informed consent, or in case of illiterate thumb prints of the participant and a signature of a witness, was obtained before interviewing in private cells. The study protocol received review and approval from the Regional Committee for Medical Research Ethics of Norway and from the National Health Research Council of Nepal.

2.4 Statistical Analyses

Age was dichotomized at the samples' median age. For ease of subgroup analyses, we dichotomized the sociodemographic measures according to our pre-understanding of the

setting and earlier studies. Group differences were examined using either Pearson's χ^2 test for categorical variables, a Student's t-test for continuous variables with a normal distribution or a Mann-Whitney U-test for variables not conferring a normal distribution. Binary logistic regression analyses (method: Enter) were performed to assess the relation of sociodemographic and clinical variables on comorbidity. Predictive ability of variables was tested by fitting the variables that showed significant group differences into logistic regression models. A p value of < 0.05 was considered significant. All analyses were performed using the Predictive Analytics SoftWare (PASW) Statistics version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

3.1 Sample characteristics and prevalence

Of the 188 participants meeting criteria for an AUD, 24 (13%) were non-dependent alcohol abusers. The median AUDIT score was 30.0 (SD= 8.6) with 150 (82%) AUD patients scoring above 20, the cutoff value set by WHO as likely alcohol dependents. A half of the sample, 97 (52%) were based outside the Kathmandu valley; 18 (including 10 Bhutanese refugee women) were foreign born. Nine were repatriates. Almost 90% were males and less than 15% were hospital attendees. The age of respondents ranged between 14 and 64 years with the mean of 35.3 (SD=10.1) years. In all, 16 were illiterate, 30 were unemployed, 62 had below average income levels, and 54 reported of not receiving adequate social support. A majority of the sample (N=107; 57%) self identified as belonging to the social class that has taboo on alcohol use (Tagadhari). Locally brewed *Raksi* was the most preferred drink (47%) followed by sealed spirits (43%). The mean career of habitual drinking was 16.8 years (SD 9.8). Nearly three fourths of the sample admitted of drinking 4 or more days per week. About 75% had used alcohol as eye-opener sometime in their drinking career, and 60% had experienced alcohol-induced blackouts.

Eighty-five (45%) of the participants met DSM-IV criteria for lifetime major depression, and 18 (21%) of them were currently in remission. Over a third 67(36%) of all AUDs patients were sufferers of at least one major depressive episode in the preceding 12-month period.

3.2 Profile of depressed and non-depressed AUD patients

As shown in table 1, AUD patients below 36 years of age were more likely than their older counterparts to have a comorbid major depression. MD was significantly less common among married patients than never married, separated or widowed patients; significantly

more depressed AUD patients were living in non-nuclear family setups. Almost one in eight (12%) depressed AUD patients either had a broken family or was living alone. Those born and living in urban areas were more depressed than rural residents. Self reported levels of education, income and adequacy of social support did not vary greatly between depressed and non-depressed individuals. Non-depressed AUD patients had a more stable employment like white collar jobs or were running own businesses.

Clinical signs of severity of alcohol-use disorders, rather than the drinking pattern, displayed stronger association with having experienced a major depression (table 1). AUD patients who used eye-openers, had experienced alcohol-induced blackouts, and reduced their priority of important activities were more likely to having experienced major depression. Additionally, more depressed than non-depressed AUD cases had faced drinking related police apprehensions. Patients drinking 2-3 days a week were least likely to be depressed. Of the considered 11 alcohol withdrawal signs, median number of withdrawal signs reported was 7 (SD=3.7) with the depressed group reporting significantly numerous signs compared to the non-depressed group. Over a third or 69 (37%) of the AUD patients reported parental, only three were maternal only, lifetime problem drinking. Parental problem drinking was significantly associated with MD.

Patients who admitted to early onset habitual drinking were significantly more likely than the late starters to have MD. Notably, average AUDIT scores did not vary markedly between depressed and non-depressed groups. Just over 70% of the females hailed from Matwali community and they scored lower in AUDIT as compared to their male counterparts. The difference observed in eye opening as background variables for depressive outcome were weakened when controlled for gender. However, rest of the findings remained consistent.

3.3 Social Taboo and MD

Of the sample, 91 (85%) Tagadharis and 73 (90%) Matwalis satisfied criteria for DSM-IV alcohol dependence. Contrary to our hypothesis, the prevalence of MD among Matwalis was higher (41%) compared with that among Tagadharis (32%) but the difference did not reach statistical significance (p=0.221).

As shown in table 1, there were significant differences between depressed and non-depressed Matwalis in terms of sociodemographic variables. Among them, age group below 36 years, those not living in marital relation, and those who lacked a stable employment were more likely to be depressed. Experiencing alcohol induced blackouts was strongly related to having MD in Matwalis. Matwalis who were abstinent for longer duration and those admitting consumption of alcohol more frequent than 2-4 times per week were more likely to have MD. In case of Tagadharis, using alcohol as eye-opener, earlier onset of habitual drinking, having experienced more numerous withdrawal signs, and scoring higher in AUDIT were related to having depression. In fact, significantly more Matwalis than Tagadharis reported of having parental problem drinking, but having a problem drinker parent was strongly associated with MD only among the Tagadharis.

Logistic regression analyses demonstrated the impact of the background variables on comorbidity. All models presented as blocks in table 2 were statistically significant ($p<0.01$). As presented, having a stable employment showed unique statistically significant contribution to the model with sociodemographic variables among Matwalis. Having experienced blackouts and longer abstinence period were retained as clinical predictors of MD among Matwalis. In case of Tagadharis, the only factor that withstood adjustment was having a parental problem drinker with an odds ratio of 7.6 (95% CI=2.6-22.3).

Discussion

The present study indicated that the rate of major depression among treatment seeking AUD patients in Nepal was around 40%, a figure lying between earlier observed extremes (37;38). Patients who experienced a major depression had shakier social truss and more often a severe alcohol-use disorder. To our knowledge, this is the first ever observation of differential occurrence of comorbidity in a society dichotomized by taboo on alcohol use. Contrary to what we had expected, belonging to a social class with a taboo on the use of alcohol was not related to higher rates of comorbid major depression in AUD patients. In fact, patients belonging to a lower social stratum with sanctioned drinking reported higher rates of depression. Predictors of major depression seemed to differ between the two social strata, with lack of stable employment and blackout experiences signifying MD in the non-tabooed class. Major depression among AUD patients in the tabooed stratum seemed to have transgenerational underpinnings.

Rates of major depression among people with an AUD have been shown to vary between different settings, especially in treatment samples. Our findings were consistent with the literature from several other countries (8;15;24;45), but the rates were higher than reported from Iceland, and Korea (46;47). These differences may partly be elucidated in terms of the use of manifold measures of depression and varying psychometrics. For example, the reported rates of meta-analysis were derived from severe depression diagnosis as measured by Hamilton depression rating scale at various time points during treatment (24). Others used DSM-III or DSM-IV criteria, differing again in their settings and sampling frame. Stringent screening criteria for DSM-IV major depressive episodes applied in our study might have actually underestimated the ‘state’ measures of depression. Although gender variation could not be assessed due to underrepresentation of females in the sample, vulnerability factors like younger age, lack of stable employment and not being in marital cohabitation were found

strongly associated with having a comorbid MD, particularly among the Matwali people. These findings support European multinational data (24) while contradicting earlier suggestions from Nepalese general population in that MD in our study was uniformly distributed across all income levels (33;48). The rates we are presenting may be influenced by treatment participation. Even in the US less than 6% AUD patients sought treatment (8). Tagadharis constituted majority (57%) of our sample despite the fact that this group represents less than a third of national population (30). Association of earlier onset of habitual drinking and a positive family history with MD among Nepalese AUD patients is consistent with available literature, but further investigation is necessary (17).

Since Tagadhari people are subjected to social taboo on alcohol consumption, occurrence of comorbid MD could be better accounted for, as would be expected for drinking behaviour, by variables other than demographics, partially comparable to other 'dry' cultures (49). This was supported by the higher prevalence of blackout experiences among Tagadharis. Interestingly, experiencing blackout was a consistent predictor of MD in the Matwali group only, pointing to the fact that even among a subset of Matwali people was drinking pattern an important correlate of comorbid MD. The length of abstinence that indicated MD among Matwalis may be a function of longer involvement in treatment owing to severity represented by longer drinking career, higher average drinking units and numerous withdrawal features. Except for familial predisposition, Matwali group displayed characteristic features of depressed AUD patients of Nepal. There are enough overlaps of these traits across the groups suggesting departure from past taboos and transition towards modern drinking culture.

Parental problem drinking which made the only consistent and meaningful correlate of MD in the Tagadhari group indicates towards the possibility of common familial factor for both the conditions. Our study supports previous findings that the adult children of problem drinkers report significantly higher symptoms of depressive affect and MD, and this seems applicable

among Nepalese problem drinkers (17;28;50). Interestingly, this phenomenon appeared unique among Tagadharis. The pathway by which paternal problem drinking moderates comorbid depression among AUD offspring is, however, not known. Exploration of risk trajectories from identification of common loci for susceptibility genes, adverse childhood experiences and externalizing disorders is necessary.

A cautious interpretation of the results of this study is necessary as the sample is representative only of treatment seeking AUD patients. The hypothesis that belonging to higher class where social forces of taboo might increase occurrence of MD and interfere with help seeking behaviour could not be supported thus emphasizing that motivation in case of the Tagadharis and severity of illness in case of the Matwalis could possibly be stronger predictors of treatment seeking. The nature of the study does not permit inferences regarding the causality and the sequential ordering of the co-occurrence. However, we propose that primary AUDs and primary MD may be more common among Matwalis and Tagadharis, respectively.

Treatment seeking AUD patients are important target for epidemiological studies of comorbidity since these individuals can provide insights into the unmet needs of the population. Clinical assessment of affective disorder in treatment seeking population, especially those with history of alcohol-use disorders, is mandatory. In local context, more tailored and broad based treatment facilities should be established in order to integrate addiction and mental health services.

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Declaration of interest

None

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Reference List

(1) **Mathers C, Fat DM, Boerma JT, World Health Organization. The global burden of disease : 2004 update. Geneva, Switzerland: World Health Organization; 2008.**

(2) **Saxena S. Alcohol, Europe and the developing countries. Addiction 1997 Mar;92 Suppl 1:S43-S48.**

(3) **Patel V. Mental health in low- and middle-income countries. Br Med Bull 2007;81-82:81-96.**

(4) **Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006 May 27;367(9524):1747-57.**

(5) **Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994 Jan;51(1):8-19.**

(6) **Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 1990 Nov 21;264(19):2511-8.**

(7) **Hasin DS, Grant BF. Major depression in 6050 former drinkers: association with past alcohol dependence. Arch Gen Psychiatry 2002 Sep;59(9):794-800.**

(8) **Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry 2004 Aug;61(8):807-16.**

(9) **Schuckit MA, Tipp JE, Bergman M, Reich W, Hesselbrock VM, Smith TL. Comparison of induced and independent major depressive disorders in 2,945 alcoholics. Am J Psychiatry 1997 Jul;154(7):948-57.**

(10) **Schuckit MA. Alcohol and depression: a clinical perspective. Acta Psychiatr Scand Suppl 1994;377:28-32.**

(11) **Sullivan LE, Fiellin DA, O'Connor PG. The prevalence and impact of alcohol problems in major depression: a systematic review. Am J Med 2005 Apr;118(4):330-41.**

(12) **Penick EC, Powell BJ, Nickel EJ, Bingham SF, Riesenmy KR, Read MR, et al. Co-morbidity of lifetime psychiatric disorder among male alcoholic patients. Alcohol Clin Exp Res 1994 Dec;18(6):1289-93.**

(13) Lynskey MT. The comorbidity of alcohol dependence and affective disorders: treatment implications. Drug Alcohol Depend 1998 Nov 1;52(3):201-9.

(14) Cornelius JR, Salloum IM, Mezzich J, Cornelius MD, Fabrega H, Jr., Ehler JG, et al. Disproportionate suicidality in patients with comorbid major depression and alcoholism. Am J Psychiatry 1995 Mar;152(3):358-64.

(15) Landheim AS, Bakken K, Vaglum P. Impact of comorbid psychiatric disorders on the outcome of substance abusers: a six year prospective follow-up in two Norwegian counties. BMC Psychiatry 2006;6:44.

(16) Sher L. Risk and protective factors for suicide in patients with alcoholism. ScientificWorldJournal 2006;6:1405-11.

(17) Conner KR, Pinquart M, Gamble SA. Meta-analysis of depression and substance use among individuals with alcohol-use disorders. J Subst Abuse Treat 2009 Sep;37(2):127-37.

(18) Chen KW, Banducci AN, Guller L, Macatee RJ, Lavelle A, Daughters SB, et al. An examination of psychiatric comorbidities as a function of gender and substance type within an inpatient substance use treatment program. Drug Alcohol Depend 2011 Apr 21.

(19) Hesselbrock MN, Meyer RE, Keener JJ. Psychopathology in hospitalized alcoholics. Arch Gen Psychiatry 1985 Nov;42(11):1050-5.

(20) Buydens-Branch, Branchey MH, Noumair D. Age of alcoholism onset. I. Relationship to psychopathology. Arch Gen Psychiatry 1989 Mar;46(3):225-30.

(21) Mason WA, Hawkins JD, Kosterman R, Catalano RF. Alcohol-use disorders and Depression: Protective Factors in the Development of Unique Versus Comorbid Outcomes. J Child Adolesc Subst Abuse 2010;19(4):309-23.

(22) Hesselbrock MN, Hesselbrock VM, Segal B, Schuckit MA, Bucholz K. Ethnicity and psychiatric comorbidity among alcohol-dependent persons who receive inpatient treatment: African Americans, Alaska natives, Caucasians, and Hispanics. Alcohol Clin Exp Res 2003 Aug;27(8):1368-73.

(23) Wang J, El-Guebaly N. Sociodemographic factors associated with comorbid major depressive episodes and alcohol dependence in the general population. Can J Psychiatry 2004 Jan;49(1):37-44.

(24) Lejoyeux M, Lehert P. Alcohol-use disorders and depression: results from individual patient data meta-analysis of the acamprosate-controlled studies. Alcohol Alcohol 2011 Jan;46(1):61-7.

(25) Cloninger CR, Bohman M, Sigvardsson S. Inheritance of alcohol abuse. Cross-fostering analysis of adopted men. Arch Gen Psychiatry 1981 Aug;38(8):861-8.

(26) Chassin L, Pitts SC, DeLucia C, Todd M. A longitudinal study of children of alcoholics: predicting young adult substance use disorders, anxiety, and depression. J Abnorm Psychol 1999 Feb;108(1):106-19.

(27) Diaz R, Gual A, Garcia M, Arnau J, Pascual F, Canuelo B, et al. Children of alcoholics in Spain: from risk to pathology. Results from the ALFIL program. Soc Psychiatry Psychiatr Epidemiol 2008 Jan;43(1):1-10.

(28) Klostermann K, Chen R, Kelley ML, Schroeder VM, Braitman AL, Mignone T. Coping Behavior and Depressive Symptoms in Adult Children of Alcoholics. Subst Use Misuse 2011 Mar 30.

(29) Compton WM, III, Cottler LB, Ben AA, Phelps DL, Spitznagel EL, Horton JC. Substance dependence and other psychiatric disorders among drug dependent subjects: race and gender correlates. Am J Addict 2000;9(2):113-25.

(30) Central Intelligence Agency. The CIA World Factbook 2011. Washington, D.C. : Skyhorse Publishing; 2010.

(31) Bishop BC. Karnali under stress : livelihood strategies and seasonal rhythms in a changing Nepal Himalaya / Barry C. Bishop. Chicago, Ill. : University of Chicago; 1990.

(32) Dhital R, Subedi G, Gurung Y.B, Hamal P. Alcohol And Drug Use in Nepal with Reference to Children. Kathmandu: Child Workers in Nepal Concerned Centre (CWIN); 2001.

(33) Kohrt BA, Speckman RA, Kunz RD, Baldwin JL, Upadhaya N, Acharya NR, et al. Culture in psychiatric epidemiology: using ethnography and multiple mediator models to assess the relationship of caste with depression and anxiety in Nepal. Ann Hum Biol 2009 May;36(3):261-80.

(34) Jhingan HP, Shyangwa P, Sharma A, Prasad KM, Khandelwal SK. Prevalence of alcohol dependence in a town in Nepal as assessed by the CAGE questionnaire. Addiction 2003 Mar;98(3):339-43.

(35) Shyangwa PM, Joshi D, Sherchan S, Thapa KB. Psychiatric morbidity among physically ill persons in eastern Nepal. Nepal Med Coll J 2009 Jun;11(2):118-22.

(36) Tausig M, Subedi S, Subedi J, Broughton C, Williams-Blangero S. The psychological disease burden in Nepal and its relationship to physical health problems. Social Behavior and Personality 2004;32(5):419-28.

(37) Khalid A, Kunwar AR, Rajbhandari KC, Sharma VD, Regmi SK. A study of prevalence and comorbidity of depression in alcohol dependence. Indian J Psychiatry 2000 Oct;42(4):434-8.

(38) Pradhan SN, Adhikary SR, Sharma SC. A prospective study of comorbidity of alcohol and depression. Kathmandu Univ Med J (KUMJ) 2008 Jul;6(23):340-5.

(39) Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, et al. The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in

conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 1988 Dec;45(12):1069-77.

(40) American Psychiatric Association. Diagnostic and statistical manual of mental disorders : DSM-IV. Washington, DC : American Psychiatric Association; 1994.

(41) Wittchen HU. Reliability and validity studies of the WHO Composite International Diagnostic Interview (CIDI): a critical review. J Psychiatr Res 1994 Jan;28(1):57-84.

(42) van Ommeren M, Sharma B, Thapa S, Makaju R, Prasain D, Bhattarai R, et al. Preparing Instruments for Transcultural Research: Use of the Translation Monitoring Form with Nepali-Speaking Bhutanese Refugees. Transcultural Psychiatry 1999 Sep 1;36(3):285-301.

(43) Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol-use disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993 Jun;88(6):791-804.

(44) Carey KB, Carey MP, Chandra PS. Psychometric evaluation of the alcohol-use disorders identification test and short drug abuse screening test with psychiatric patients in India. J Clin Psychiatry 2003 Jul;64(7):767-74.

(45) Hasegawa K, Mukasa H, Nakazawa Y, Kodama H, Nakamura K. Primary and secondary depression in alcoholism: clinical features and family history. Drug Alcohol Depend 1991 May;27(3):275-81.

(46) Tomasson K, Vaglum P. A nationwide representative sample of treatment-seeking alcoholics: a study of psychiatric comorbidity. Acta Psychiatr Scand 1995 Nov;92(5):378-85.

(47) Cho MJ, Hahm BJ, Suh T, Suh GH, Cho SJ, Lee CK. Comorbid mental disorders among the patients with alcohol abuse and dependence in Korea. J Korean Med Sci 2002 Apr;17(2):236-41.

(48) Tausig M, Subedi S, Broughton CL, Subedi J, Williams-Blangero S. Measuring community mental health in developing societies: evaluation of a checklist format in Nepal. Int J Soc Psychiatry 2003 Dec;49(4):269-86.

(49) Paljarvi T, Koskenvuo M, Poikolainen K, Kauhanen J, Sillanmaki L, Makela P. Binge drinking and depressive symptoms: a 5-year population-based cohort study. Addiction 2009 Jul;104(7):1168-78.

(50) Hill SY, Shen S, Lowers L, Locke-Wellman J, Matthews AG, McDermott M. Psychopathology in offspring from multiplex alcohol dependence families with and without parental alcohol dependence: A prospective study during childhood and adolescence. Psychiatry Research 2008 Aug 15;160(2):155-66.

Table 1. Socio-demographic and clinical features of 12 month depressed and non-depressed Nepalese patients with an alcohol-use disorder by total, and subsample of alcohol related non-tabooed (Matwali) and tabooed (Tagadhari) group.

		Total (N=188)			Matwali (N=81)			Tagadhari (N=107)		
		Non-depressed (n=121)	Depressed (n=67)	P value	Non-depressed (n=48)	Depressed (n=33)	P value	Non-depressed (n=73)	Depressed (n=34)	P value
Socio- demographics										
Age below 36 years	N (%)	**60 (49.6)**	**44 (65.7)**	**0.046**	**22 (45.8)**	**24 (72.7)**	**0.023**	38 (52.1)	20 (58.8)	0.539
Male gender	N (%)	108 (89.3)	60 (89.6)	1.000	41 (85.4)	26 (78.8)	0.552	67 (91.8)	34 (100)	0.174
Urban origin	N (%)	**60 (50.0)**	**45 (67.2)**	**0.031**	30 (63.8)	25 (75.8)	0.330	30 (41.1)	20 (58.8)	0.100
Not cohabitation	N (%)	**38 (31.4)**	**35 (52.2)**	**0.008**	**15 (31.3)**	**19 (57.6)**	**0.023**	23 (31.5)	16 (47.1)	0.135
Non-nuclear family	N (%)	48 (39.7)	35 (52.2)	0.125	17 (35.4)	17 (51.5)	0.174	31 (42.5)	18 (52.9)	0.405
Education lower than 7 years	N (%)	36 (29.8)	18 (26.9)	0.738	18 (37.5)	13 (39.4)	1.000	18 (24.7)	18 (24.7)	0.316
Inadequate social support	N (%)	33 (27.3)	21 (31.3)	0.615	12 (25.0)	11 (33.3)	0.459	21 (28.8)	21 (28.8)	1.000
Unstable or no employment	N (%)	**42 (35.0)**	**35 (52.2)**	**0.030**	**13 (27.7)**	**21 (63.6)**	**0.003**	29 (39.7)	29 (39.7)	1.000
Low personal income (<60,000 Nepalese Rupees/year)	N (%)	36 (34.3)	19 (33.3)	1.000	19 (44.2)	14 (51.9)	0.625	17 (27.4)	17 (27.4)	0.306
Clinical characteristics										
Institution (Rehabilitation centre)	N (%)	102 (84.3)	59 (88.1)	0.524	38 (79.2)	28 (84.8)	0.574	64 (87.7)	31 (91.3)	0.749
Beverage (Industrial)	N (%)	55 (45.5)	36 (53.7)	0.290	18 (37.5)	14 (42.4)	0.817	37 (50.7)	22 (64.7)	0.213
Drinking frequency (>2-4 days every month)	N (%)	108 (89.3)	55 (82.0)	0.183	**47 (97.9)**	**28 (84.8)**	**0.039**	61 (83.6)	27 (79.4)	0.597
Eye opener	N (%)	**85 (70.8)**	**56 (84.8)**	**0.034**	36 (76.6)	25 (75.8)	1.000	**49 (67.1)**	**31 (93.9)**	**0.003**
Blackouts	N (%)	**63 (53.4)**	**51 (78.5)**	**0.001**	**21 (45.7)**	**25 (78.1)**	**0.005**	**42 (58.3)**	**26 (78.8)**	**0.049**
Reduced important social or occupational activities	N (%)	**62 (51.2)**	**46 (68.7)**	**0.022**	22 (45.8)	21 (63.6)	0.174	40 (54.8)	25 (73.5)	0.089
Alcohol related police apprehensions	N (%)	**36 (29.8)**	**33 (49.3)**	**0.011**	16 (33.3)	17 (51.5)	0.114	20 (27.4)	16 (47.1)	0.051
Parental problem drinking	N (%)	**33 (27.3)**	**36 (53.7)**	**0.000**	20 (41.7)	18 (54.5)	0.268	**13 (17.8)**	**18 (52.9)**	**0.000**
Age at onset of habitual drinking	mean, SD	**19.12 (6.33)**	**17.09 (6.33)**	**0.037**	17.04 (5.87)	16.21 (6.09)	0.540	**20.48 (6.29)**	**17.94 (6.52)**	**0.048**
Drinking career in years	mean, SD	16.97 (10.09)	16.49 (9.43)	0.752	18.73 (10.04)	15.67 (9.52)	0.172	15.81 (10.01)	17.29 (9.41)	0.468
Daily drinking units	mean, SD	12.28 (5.43)	12.90(6.07)	0.527	12.9 (5.28)	12.74 (6.48)	0.921	11.97 (5.52)	13.03 (5.86)	0.404
Current abstinence in days	mean, SD	34.21 (30.71)	43.95 (34.31)	0.061	**30.68 (28.99)**	**56.27 (33.88)**	**0.001**	36.56 (31.78)	33.61 (31.61)	0.668
Number of withdrawal signs	mean, SD	**5.37 (3.64)**	**6.88 (3.71)**	**0.009**	5.78 (3.88)	6.81 (3.81)	0.248	**5.09 (3.48)**	**6.94 (3.66)**	**0.015**
AUDIT average score	mean, SD	2.73 (0.81)	2.90(0.94)	0.188	2.82 (0.78)	2.70 (1.04)	0.590	**2.67 (0.83)**	**3.10 (0.81)**	**0.015**

P values are two tailed calculated by χ^2 test, and student t-test or Mann Whitney U-test in case of continuous variables; SD: standard deviation

Table 2. Odd ratio (OR) with 95 % confidence interval (CI) for reporting 12-month major depression by the total group of alcohol-use disorder patients within treatment and for the Matwali and Tagadhari community in Nepal according to socio-demographic and clinical characteristics

	Total		Matwali		Tagadhari	
	OR (95% CI)	aOR (95% CI)[a]	OR (95% CI)	aOR (95% CI)[a]	OR (95% CI)	aOR (95% CI)[a]
Socio-demographic		**Block I**		**Block III**		
Age <36 Years	1.95 (1.05-3.61)*	1.38 (0.69-2.80)	3.15 (1.22-3.00)*	2.37 (0.80-7.03)	1.32 (0.58-3.00)	
Urban Origin	2.05 (1.09-3.81)*	1.89(0.99-3.56)	1.77 (0.66-4.78)		2.05 (0.90-4.68)	
Cohabitation (No)	2.39 (1.29-4.42)**	1.76 (0.86-3.61)	3.99 (1.19-7.50)*	1.34 (0.43-4.23)	1.93 (0.84-4.45)	
Stable employment (No)	2.03 (1.11-3.73)*	1.63 (0.85-3.13)	4.57 (1.76-11.89)**	3.71 (1.27-10.83)*	1.06 (0.46-2.43)	
Clinical characteristics		**Block II**		**Block IV**		**Block V**
Eye-opener	2.31 (1.06-5.03)*	1.34 (0.52-3.45)	0.96 (0.37-2.71)		7.59 (1.68-34.40)**	3.89 (0.57-26.39)
Blackout	3.18 (1.59-6.36)***	2.68 (1.18-6.08)*	4.25 (1.53-11.78)**	4.07 (1.27-13.02)*	2.65 (1.10-6.91)*	1.52 (0.36-6.38)
Drinking frequency (>2-4/month)	0.55 (0.24-1.29)		0.12 (0.01-1.07)		0.76 (0.27-2.20)	
Average drinks/day	1.02 (0.96-1.08)		1.00 (0.91-1.09)		1.03 (0.96-1.12)	
Abstinent period	1.01 (0.99-1.02)		1.03 (1.01-1.04)**	1.02(1.01-1.04)**	1.00 (0.99-1.01)	
Altered priorities	2.08(1.11-3.90)*	1.21 (0.54-2.7)	2.07 (0.83-5.13)		2.29 (0.94-5.58)	
Number of withdrawal signs	1.12 (1.03-1.22)**	1.06 (0.95-1.18)	1.07 (0.95-1.21)		1.17 (1.03-1.33)*	1.0(0.93-1.32)
Parental problem drinking	3.10 (1.66-5.79)***	3.58 (1.79-7.18)***	1.68 (0.69-4.11)		5.19 (2.11-12.80)***	7.657(2.57-22.31)***
Drinking career	1.00 (0.97-1.03)		0.97 (0.92-1.02)		1.02 (0.98-1.06)	
Police apprehensions	2.29 (1.24-4.25)**	1.58 (0.78-3.20)	2.13 (0.86-5.27)		2.36 (1.01-5.50)*	1.91 (0.61-6.00)
AUDIT average score	1.28 (0.89-1.84)		0.86 (0.52-1.44)		2.00 (1.13-3.54)*	1.19 (0.44-3.17)

*P<0.05, **P<0.01, ***P<0.001; [a] aOR indicates adjusted odds ratios after adjusting for other variables within the block that were significantly related to being depressed