ORIGINAL ARTICLE
Prognostic Factors of 2-year Outcomes of Patients with Comorbid Bipolar Disorder or Depression with Alcohol Dependence: Importance of Early Abstinence
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Abstract — Aims: To investigate the prognostic factors that determine 2-year outcomes in a group of alcohol-dependent patients with depression or bipolar disorder who were treated in an intensive 4-week inpatient programme. Methods: This was a longitudinal study of an inpatient treatment cohort of dual affective disorder and alcohol-dependent patients, in Dublin, Ireland. Measurements included baseline demographics with follow-up measurements at discharge, 3 months, 6 months and 2 years after treatment, including alcohol consumption, depression, mania/elation, anxiety, craving, drug use and sample blood tests. Factor and regression analysis of multiple variables was carried out to predict outcomes. Results: A total of 189 participants with alcohol dependence and comorbid depression (n = 101) or bipolar disorder (n = 88) were followed over 2 years after discharge from treatment. Retention rate was 76% over 2 years. Early abstinence (at 6 months) predicted better abstinence overall at 2 years; and bipolar alcoholics had a better outcome in drinks per drinking day than depressed alcoholics at 2 years. Younger participants (age 18–30 years) did relatively worse than middle-age (30–50 years) and older (51+ years) participants in measures of abstinence and number of drinks per drinking day at 2 years; and females did better than males in number of drinks per drinking day at 2 years. Conclusion: Dual diagnosis of alcohol dependence and depression or bipolar disorder may be treated together with intensive intervention and follow-up, and various prognostic factors including early abstinence emerge over time that influence outcomes over 2 years.

INTRODUCTION
Dual diagnoses in general, and comorbid alcohol use disorders (AUDs) and affective disorders (major depression and bipolar disorder) in particular, are an undertreated and under-researched area of psychiatry. While there is evidence that the combination of AUD and affective disorders represent 50% of the AUDs and 30% of affective disorders presenting for treatment (Hasin et al., 2007), the majority of treatment studies focus on one of the disorders alone. This has led to co-morbidity being either neglected or underemphasized in outcome-based research, allowing traditional single diagnosis outcome studies to determine common practice.

Long-term-outcome studies are rare in AUDs, and those that exist have significantly influenced thinking in the field (Vaillant, 1996; Powell et al., 1998; Schuckit et al., 2004). Long-term-outcome studies in affective disorders have been more common and have largely focused either on bipolar disorder (Judd et al., 2002) or on depression (Keller and Boland, 1998; Kennedy et al., 2003) alone. To date, there have been few long-term-outcome studies of dual disorders (Xie et al., 2010), and none, apart from this research group (Farren and McElroy, 2008), of outcomes in dual AUDs and affective disorders. Similarly, treatment studies either with psychotherapy (Weiss et al., 2007) or with pharmacotherapy (Salloum et al., 2005; Pettinati et al., 2010), of dual AUDs and affective disorders, are few and also characterized by a relatively short duration of follow-up. Our earlier reports found that some baseline factors including organization of aftercare, baseline anxiety levels and baseline AUDIT scores predicted relapse to alcohol at 3 and 6 months (Farren and McElroy, 2010), with gender having influence at a preliminary 2-year analysis (Farren et al., 2011).

Bipolar disorder and depression have traditionally been regarded as separate diagnoses and treated as such. The boundaries between these diagnoses are increasingly being questioned (Akiskal et al., 1995; Smith et al., 2008; Angst et al., 2010), and consequently, questions naturally arise about the similarities and differences in treatment approaches between the two disorders. Our programme does not distinguish between the diagnoses for psychotherapeutic and after-care purposes. Other reports examining bipolar alcoholics (Frye et al., 2003) and depressed alcoholics (Hirschfeld et al., 1990) suggest that these disorders may have different long-term outcomes, so it is possible that outcome differences may emerge at 2 years.

Age also has a profound impact upon treatment response to AUDs, younger people responding poorly to many different interventions, relative to older subject (Kim et al., 2012). It is generally assumed that in affective disorders, particularly with bipolar disorder, early age of onset is a negative prognostic factor (Carlson et al., 2002). This would suggest that it might be expected that early onset of a dual diagnosis may suggest a more difficult therapeutic journey and a poorer prognosis.

It is important to identify those factors that influence short- and long-term outcomes in comorbid alcohol and affective disorders. This study is a continuation of a previously published study identifying predictive prognostic factors for dual alcohol and affective disorder patients in early treatment (Farren and McElroy, 2010), and extends a preliminary analysis of the 2-year findings (Farren et al., 2011)

METHODS
The sample in the current study included 189 people with a diagnosis of a mood disorder (major depression or bipolar disorder) with co-occurring alcohol dependence. The sample comprised 51% females and 49% males with an age range from 17 to 76 years and a mean age of 43. The study
received ethical approval from the ethics committee at St. Patrick’s University Hospital, Dublin. All persons referred by their GP or internal psychiatrist for a calendar year on the basis of a possible dual diagnosis were assessed for suitability for the dual diagnosis programme. Patients were eligible if they met the DSM-IV (SCID) (First et al., 2004) criteria for alcohol dependence and for mania/hypomania or major depression. Informed consent was obtained to take part in the programme and the parallel research project. All recruits over the first year of the programme were included and followed up at four time periods (discharge, 3 months, 6 months and 2 years after treatment).

The programme

Founded in 2003, the dual diagnosis programme at St. Patrick’s University Hospital provides patients with a mood disorder and a co-occurring substance use problem with a structured inpatient treatment programme that addresses both illnesses (Farren and McElroy, 2008). The programme itself involved three main stages:

1. detoxification and mood stabilization,
2. the 4-week inpatient programme and
3. aftercare was offered to all patients on a weekly basis for the first 2 months, bi-weekly for the second 2 months and monthly for the last 2 months.

Measures

All the patients underwent assessment upon completion of detoxification from alcohol and on stabilization of mood. All the subjects were at least 7 days from their last drink at baseline. Assessments conducted by a single psychologist included: the SCID Research version (First et al., 2004), demographic details, a timeline follow-back (Sobell et al., 1988), Young Mania Rating Scale (YMRS, Young et al., 1978), Beck Depression Inventory (BDI, Beck et al., 1961), Beck Anxiety Inventory (Beck et al., 1988), Obsessive Compulsive Drinking Scale (Anton et al., 1996), Alcohol Use Disorder Test (AUDIT, Saunders et al., 1993) and the Drug Abuse Screening Test (DAST, Skinner, 1982). All the participants also took a urinary drug screen for illicit substances and underwent blood tests, including the mean corpuscular volume, gamma glutamyl transferase and aspartate aminotransferase.

Upon completion of the 4-week programme, the patients were discharged, provided their moods had been stabilized. At 3 and 6 months after treatment, the patients were contacted and asked to return to the hospital to complete the battery of assessments again. At 2-years after discharge from treatment, the participants completed the battery of assessments again with the addition of the AUDIT and the DAST.

Statistical analyses

All statistical analyses were conducted using Statistical Package for Social Sciences Version 18. The database was screened and cleaned to identify any errors or outliers in the data and to assess assumptions of the statistical analyses used. Demographic data and data at the 2-year time point were used in the analysis. Chi-square analyses, t-tests and analysis of variances (ANOVs) were conducted to establish differences between groups and to look at trends over time. A logistic regression was conducted to examine the utility of the proposed model in predicting categorical variables including abstinence. A standard multiple regression was conducted to examine the utility of a proposed model in predicting continuous variables, including average number of alcoholic units per drinking day.

RESULTS

Of the 189 baseline participants who were eligible for follow-up, 94.7% were followed up at 3 months and 86.6% were followed up at 6 months. An overall retention rate of 75.1% was observed at 2-year follow-up. Of the remaining 24.9%, 2.6% had died, 2.6% had illness, 14.8% could not be contacted, 1.6% refused to participate and 3.2% were

<table>
<thead>
<tr>
<th>Age (n)</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Gender</th>
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<tr>
<td></td>
<td>≤30</td>
<td>31–50</td>
<td>51+</td>
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<tr>
<td>Age (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 years</td>
<td>20</td>
<td>19</td>
<td>8*</td>
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<tr>
<td>31–50 years</td>
<td>42</td>
<td>45</td>
<td>51*</td>
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<tr>
<td>51+ years</td>
<td>39</td>
<td>24</td>
<td>38</td>
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</tbody>
</table>

Table 1. Characteristics of the participants at 2 years delineated by age, gender and diagnosis

*Significant difference between the groups (P < 0.01).
†Significant difference between the groups (P < 0.05).
unavailable for participation. There were strenuous efforts to contact all participants, through phone calls, written communication and liaison with treating general practitioners.

**Descriptive analyses**

The baseline characteristics for the current population at 2 years are described in Table 1. The characteristics are described within subgroups of age, diagnosis and gender.

Significant differences between the diagnosis groups indicated that those with bipolar disorder scored significantly higher on the DAST [t (79.97) = 1.99, P = 0.49]; significantly more participants with bipolar disorder were using psychiatric medications [χ² (1) = 5.56, P = 0.018] and significantly more participants with bipolar disorder had a family history of psychiatric problems [χ² (1) = 7.62, P = 0.006]. There were significantly more men than women in paid employment [χ² (1) = 7.19, P = 0.007].

Across the three age, there were significantly more men in the youngest age group [χ² (2) = 17.62, P = 0.00]; aftercare attendance increased significantly with age [χ² (2) = 8.73, P = 0.013]; DAST scores were significantly higher for the youngest age group [F (2) = 6.86, P = 0.001]; significantly fewer participants in the middle age group used psychiatric medication [χ² (1) = 7.70, P = 0.021]; significantly fewer participants in the eldest age group were in paid employment [χ² (2) = 18.13, P = 0.000], and significantly fewer participants in the youngest age group had a family history of alcohol problems [χ² (1) = 5.98, P = 0.05]. Those in the youngest age group and females were fewer in number than any other of these subcategories; however, this does not impact on the minimum number of participants required in each cell for subsequent regression analyses.

**Exploratory/preliminary analyses**

Chi-square and t-test analyses were carried out for abstinence and average number of units per drinking day and found no significant difference between the Bipolar I and II groups. Therefore, those with a diagnosis of Bipolar I or II are treated as one group in these analyses. At baseline the depressed group had 42.7 (±SD 30.6) drinking days in the previous 90, and the bipolar group had 38.3 (±32.5) drinking days, P = ns. The depressed group had 11.6 (±7.9) units per drinking day at baseline and the bipolar group had 11.9 (±8.9) units, P = ns. The depressed group had a baseline BDI of 25.5 (±8.7), and the bipolar group scored 23.7 (±11.8), P = ns. The bipolar group had a YMRS score of 9.9 (±7.7) at baseline, significantly higher than the depressed group at 0.7 (±2), P < 0.001.

Chi-square analyses examined data from 3 months, 6months and 2 years to establish trends over time with regard to the outcome variables of abstinence at 2 years and average number of units per drinking day at 2 years. On examination of variables at 3 and 6 months, no variables (age, gender, diagnosis, aftercare and abstinence at 3 and 3 months) had a significant relationship with either of the outcomes. However, significant differences were found at 2-year follow up (see Table 2). A significantly greater number of those who were abstinent at 3 months [χ² (1) = 17.93, P = 0.001] and 6 months [χ² (1) = 11.74, P = 0.001] were also abstinent at 2 years. A significantly greater percentage of those participants who were attending aftercare at 2 years were abstinent at 2 years [χ² (1) = 3.97, P = 0.046]. People who were abstinent at 3 months were drinking a significantly lower average number of units per drinking day at 2 years than those who had not been abstinent at 3 months [t (139) = 2.87, P = 0.005].

Participants who had a diagnosis of bipolar disorder were drinking a significantly greater average number of units per drinking day at 2-year follow-up than those with a diagnosis of depression [t (109.11) = 2.10, P = 0.038]. There were significantly more women who were abstinent than men [χ² (1) = 10.91, P = 0.002]. There were significantly fewer

<table>
<thead>
<tr>
<th>Table 2. Significant characteristics according to outcome measures at 2 years</th>
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<tbody>
<tr>
<td>Abstinence</td>
</tr>
<tr>
<td>Abstinent at 3 months*†</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Abstinent at 6 months*</td>
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<tr>
<td>No</td>
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<tr>
<td>Attending aftercare at 2 years*</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>Bipolar</td>
</tr>
<tr>
<td>Age*†</td>
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<tr>
<td>31–50 years</td>
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<tr>
<td>51+ years</td>
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<tr>
<td>Gender*†</td>
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<tr>
<td>Male</td>
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</tbody>
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*Chi-square analyses (outcome = abstinence) indicate a significant difference (P < 0.05).
†T-test analyses (outcome = avg. no. units) indicate a significant difference (P < 0.05).
‡ANOVA analyses (outcome = avg. no. units) indicate a significant difference (P < 0.05).

| Table 3. Predictor variables associated with abstinence at 2 years* |
|---------------------|---------------------|---------------------|---------------------|
| Abstinence at 3 months | 2.91 | 0.93–9.11 | 0.07 |
| Abstinence at 6 months | 4.66 | 1.53–14.16 | 0.01** |
| Aftercare | 0.62 | 0.17–2.24 | 0.47 |
| Diagnosis | 1.94 | 0.66–5.73 | 0.23 |
| 31–50 years of age | 1.11 | 1.11–26.78 | 0.04* |
| 51+ years of age | 5.17 | 1.69–62.41 | 0.01** |
| Gender | 2.06 | 0.72–5.89 | 0.18 |
| Medication | 1.99 | 0.44–9.15 | 0.37 |
| Employed | 1.29 | 0.39–4.21 | 0.67 |
| Hx alcohol | 0.77 | 0.24–2.49 | 0.66 |
| Hx psychiatric | 1.27 | 0.39–4.09 | 0.69 |
| Years in education | 0.99 | 0.82–1.21 | 0.95 |
| Young mania | 1.05 | 0.68–1.62 | 0.84 |
| DAST | 0.80 | 0.55–1.15 | 0.22 |

*Values are ORs obtained from the logistic regression model. An OR of <1 indicates a lower likelihood of achieving abstinence.
†Categorical variables.
‡Continuous variables.
§Significant at P < 0.05.
**Significant at P < 0.01.
participants in the youngest age group who were abstinent [χ² (2) = 15.25, P = 0.001]. Abstinence was greatest in the oldest age group. Men were found to have a significantly higher average number of units consumed per drinking day [t (84.61) = 3.99, P = 0.001]. The participants in the youngest age group consumed a significantly greater number of units per drinking day [F (2) = 6.46, P = 0.002].

Regression analyses

On the basis of preliminary analyses of the data, factors were identified that have statistical and clinical importance for both the outcome variables. In order to identify those that have the greatest predictive ability, regression analyses were chosen to elicit this information.

A logistic regression was used to identify variables associated with alcohol abstinence using a Forced Entry method as there was no existing theoretical approach. A summary of the results is presented in Table 3. Baseline alcohol consumption of number of drinking days was not a predictor of treatment outcome. Baseline depression or mania scores were not predictive of treatment outcome. Abstinence at 6 months predicts that a participant is almost five times more likely to be abstinent at 2 years. On examination of the odds ratio for age and abstinence at 6 months, we can see that a participant who is in the older age groups and was abstinent at 6 months was more likely to be abstinent at 2 years. Conversely, being in the youngest age group increases the likelihood that a participant will be drinking at 2 years. Those in the middle age group of 31–50 years of age were more likely to be abstinent at 2 years also. Overall, this model correctly predicted 78% of the cases.

A standard multiple regression analysis was carried out to assess the predictive utility of the core variables for a second outcome variable, that is, average number of alcohol units per drinking day. A second model using multiple regression analysis examining the number of drinking days as an outcome was not supported. The assumptions of multicollinearity, outliers, normality, linearity, homoscedasticity and independence of residuals were examined. Table 4 summarizes the findings for the multiple regression.

The model reaches statistical significance. On examination of individual factors, gender was the strongest contributor to the model with men more likely to drink a greater average number of units per drinking day than women. We can see that being in the youngest age group, male and suffering from bipolar disorder predict a greater level of alcohol consumption. Those that were in the 31–50 years of age group contributed significantly to the model in predicting alcohol consumption. Neither baseline alcohol consumption, nor baseline depression or mania scores were predictive of outcomes in drinks per drinking day.

DISCUSSION

This study found that early abstinence was a predictive factor for abstinence at 2 years, suggesting that early efforts at recovery appear to maintain benefit into the future. This is consistent with some of the predictive factors for alcohol dependence alone, where early abstinence and treatment engagement is predictive of long-term recovery (Haver et al., 2001; Bottledemer and Soyka, 2005) and also consistent with the prognosis for some affective disorders, where evidence for completeness of remission in early recovery is associated with better long-term outcomes (Paykel et al., 1995). Complete abstinence may not be as necessary in dual diagnosis as it is in alcohol dependence alone, with a minority of patients drinking a small number of drinks per drinking day and still not having a major deterioration in function. With the information from this study, our group has subsequently intensified efforts to increase abstinence in the early post-discharge period. Early rehospitalization for relapse has been instituted, and other interventions including text messaging support in the first 3 months also assessed, with some notable success (Agyapong et al., 2012). Aftercare attendance lessens in impact over time. While it has a significant impact upon early recovery, aftercare attendance falls over time, and correspondingly its influence as an outcome variable also falls. At the 2-year point, a large majority of patients no longer attend aftercare (~80%), and any potential influence upon abstinence is difficult to calculate because of the small percentage of attendees.

There was a significantly better outcome in the depressed alcoholic sample regarding drinks per drinking day. This difference in outcome between type of mood disorder emerges over time, and was not found at 3 and 6 months after discharge (Farren and McElroy, 2008). However, the overall figures for abstinence and drinks per drinking day suggest that the groups can be treated together in a dual diagnosis programme and that benefits continue after discharge. There is recent evidence for differences between depression and bipolar disorder based upon the characteristics of the depressive episodes (Mitchell et al., 2011) as well as obvious syndromal characteristics (DSM-IV), but many reports emphasize the similarities between the two disorders (Akiskal et al., 1995; Angst et al., 2010; Smith et al., 2011), particularly in situations of co-morbidity with substance use disorders (Merikangas et al., 2008) suggesting the possibility of a spectrum disorder (Smith et al., 2008). Overall, this study suggests that their psychoeducational and addiction treatments may be undertaken together successfully.

This study gives evidence for a significant difference in outcomes relative to age of participants, with young people between 18 and 30 having a significantly worse prognosis than those who were middle aged or older. Age does appear to have significant effect upon prognosis in alcohol dependence alone, with young people relapsing earlier in treatment.

Table 4. Predictor variables associated with average number of alcohol units consumed per drinking day at 2 yearsa,b

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>Significance</th>
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<tr>
<td>Aftercare attendancec</td>
<td>-0.06</td>
<td>0.476</td>
</tr>
<tr>
<td>Diagnosisc</td>
<td>0.17</td>
<td>0.036*</td>
</tr>
<tr>
<td>Age 31–50 yearsc</td>
<td>-0.27</td>
<td>0.015*</td>
</tr>
<tr>
<td>Age 51+ yearsc</td>
<td>-0.21</td>
<td>0.058</td>
</tr>
<tr>
<td>Genderf</td>
<td>0.28</td>
<td>0.001**</td>
</tr>
</tbody>
</table>

a Beta values are the standardized coefficients and indicate the unique contribution of a variable to explaining the outcome.

b The overall model is significant [F (5) = 6.14, P < 0.05].

c Categorical variables.

*Significant at P < 0.05.

**Significant at P < 0.01.
than older age (Kim et al., 2012), but this has not been found consistently (Rice et al., 1993; Bottlender and Soya, 2005). Age does not appear to be a significant prognostic factor in a previous alcoholic dual diagnosis population (Kranzer et al., 1996), but most dual diagnosis studies are limited by small numbers and relatively short duration of follow-up (Salloum et al., 2005; Pettinati et al., 2010). One of the causes of youth being a negative prognostic factor in alcoholism alone may be that early-onset (<25 years) alcoholics have an increased range of difficulties and a poorer prognosis relative to older-onset (>25 years) alcoholics (Babor et al., 1992; Fils-Aime et al., 1996). Part of the explanation for the poorer response may be the increased social pressure in recent times on younger adults to drink earlier and drink more (Smyth et al., 2011). There is also evidence that the human brain continues to mature even as far as age 30 (Dosenbach et al., 2010), and that the prefrontal cortex, implicated in addictive disorders (Volkow et al., 2007; Goldstein and Volkow, 2011), undergoes one of the longest periods of development of any brain region (Diamond, 2002), and this developmental delay may contribute to the poor response to treatment in the younger age group. Finally, there is evidence for alcohol itself causing damage to adolescent brain, and this damage may be to a number of areas, such as the prefrontal cortex and may lead to subtle neuronal reorganization, which may have implications in therapeutic response (Tapert et al., 2004).

Effects of age were not found in mood-related outcomes, either in the depressed or the bipolar group in this study. While there is evidence for effect of early age of onset of bipolar disorder having a negative effect upon prognosis (Carlson et al., 2002), and evidence for a recent increase in risk in middle age for development of depression (Hasin et al., 2005), there is no evidence for any effect of age of subjects upon prognosis in either bipolar disorder or depression. Thus, the poorer response in the younger cohort appears to have been driven by the poorer alcohol recovery component of the disorders rather than by the affective component.

It is disappointing that few baseline features were predictive of treatment outcomes at 2 years. An analysis of predictive factors for relapse at early stages in the research found that high baseline anxiety predicted relapse by 3 months and high baseline AUDIT scores predicted relapse at 3 and 6 months, while planning for aftercare predicted non relapse at 3 and 6 months (Farren and McElroy, 2010). The effects of these factors wane by 2 years and then the issues of gender, age, diagnosis and early abstinence emerge. Thus, short- and long-term outcomes have different predictive factors in this population.

This study has a number of limitations. The patients were sufficiently motivated to engage in a 4-week inpatient programme, and these results may not be applicable to less motivated patients. The groups studied were racially homogenous and relatively well educated, and thus, findings may not apply to other countries, racial groups and educational levels. The percentage of the original cohort followed up at 2 years, while relatively high for this diagnostic group, leaves the possibility of a different outcome in the non-respondents. The non-respondents did not differ from the respondents in any of the important variables identified in the analysis.

Nonetheless, this study does give some evidence for the benefits of well-designed focused dual diagnosis therapeutic interventions and demonstrates that various prognostic factors influence outcomes over time, and these factors have a different influence over 2 years relative to earlier assessments.

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REFERENCES


