Relationship between prescribed psychotropic medications and co-ingested alcohol in intentional self-poisonings

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Background
Acute alcohol consumption is a major risk factor for suicide, therefore investigating factors associated with alcohol-related self-harm warrant attention.

Aims
To investigate the influence of prescribed psychotropic medications on the odds of co-ingesting alcohol preceding or during intentional efforts to self-poison.

Method
A cross-sectional analysis of consecutive hospital presentations following intentional self-poisoning was conducted. A total of 7270 patients (4363 women) aged 18–96 were included.

Results
The odds of alcohol co-ingestion were increased in those not prescribed any medication (odds ratio (OR) = 1.27, 99% CI 1.10–1.46, \( P < 0.001 \)) and in impulsive self-poisonings (OR = 1.39, 99% CI 1.11–1.74, \( P < 0.001 \)). Odds were decreased in those prescribed anticonvulsants (OR = 0.69, 99% CI 0.51–0.93), antipsychotics (OR = 0.55, 99% CI 0.45–0.66) and antidepressants (OR = 0.87, 99% CI 0.77–0.99).

Conclusions
Findings indicate that being medicated for a psychiatric illness may reduce the likelihood of alcohol consumption during times of acute distress, hence perhaps may reduce the risk of intentional self-poisoning.

Declaration in interest
None.

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Acute use of alcohol is strongly associated with the risk of propelling suicidal thoughts and ideation into an attempt on life. Studies investigating alcohol as a proximal risk factor for suicide have demonstrated risks greater than, and independent of, those associated with alcohol use disorders (AUD), which are heavily implicated suicidal risk factors. Drinking alcohol immediately preceding a suicide attempt has been associated with a 6-fold risk of suicide compared with lower levels of drinking and a 16-fold risk compared with not drinking. These figures are alarming considering that over a third of suicides from a national US sample \((n = 57,813)\) had a positive blood alcohol concentration.

Hence, addressing the risks associated with acute episodes of drinking has been suggested to be one of the greatest tools to prevent suicide attempts yet a thorough understanding of mediating factors associated with this behaviour is limited. Previous studies have identified general characteristics of people more likely to ingest alcohol before/during suicidal behaviour including male gender, middle age and race/ethnicity. Although this information is important in terms of public health targeting, these factors cannot be changed and therefore this knowledge provides limited options in terms of individual intervention strategies. There remains a need to investigate modifiable risk factors for suicide and self-harm. One avenue for investigation is the interaction between alcohol and use of psychotropic medications, prescriptions for which are highly prevalent in Western societies and increasing.

The neurobiological systems targeted by psychotropic medications largely overlap those that are implicated in the individual propensity for alcohol-related behaviours, hence the impact of these medications on alcohol use warrants attention. The aim of the present study was to investigate the relationship between prescribed psychotropic medication and co-ingested alcohol at time of self-harm using a cohort of people who presented, or were admitted, to hospital for treatment of intentional self-poisoning. As a result of the effects of psychotropic medications on neurobiological systems involved in alcohol-related behaviours, we hypothesised that those who co-ingest alcohol may be discernible based on their prescribed medications. The results of the study will provide insight into whether psychotropic medications are mediating factors towards proximal alcohol use before self-poisoning.

Database
Data for this analysis were extracted from a cohort of consecutive presentations following poisoning managed by the Hunter Area Toxicology Service (HATS) between January 1987 and February 2014. HATS has direct clinical responsibility for all adult patients with poisoning in all hospitals in greater Newcastle and provides a tertiary referral service to Maitland and the Hunter Valley, covering a population of around 500 000. A structured data collection form is used by HATS for prospective collection of information on all patients who present, including demography, drugs and doses ingested as part of poisoning, prescribed medications, type of poisoning (i.e. intentional, recreational, accidental, environmental, envenomation or iatrogenic) and serious illness. If poisoning is intentional, the patient is asked whether it was premeditated. During an additional assessment, psychiatric diagnoses are made according to the DSM-III-R or DSM-IV by the liaison psychiatry team and confirmed via case consensus.

Data are entered routinely into a fully relational research Microsoft Access database, separate to the hospital’s main medical record system. This study has been approved by the Hunter New England Area Health Service Human Research Ethics Committee.
Inclusion criteria

Records were extracted from the database if they satisfied the following criteria: (a) the self-poisoning was intentional; (b) a psychiatric evaluation was conducted; and (c) the patient was aged over 18 years. Records that satisfied these inclusion criteria were used in analysis 1. In order to make direct comparisons across psychotropic medication classes without possible confounding of polypharmacy, patients that were using more than one prescribed medication or those who were prescribed a medication that was not classed as a psychotropic were then further excluded for analysis 2.

Records were split based on the primary outcome, those who co-ingested alcohol (Alc+) v. those who did not (Alc−). Alcohol was recorded as a co-ingested substance only if it was ingested either immediately preceding the poisoning or as a co-ingested substance during the poisoning. Age categories were chosen for comparison with a previous study6 as follows: 18–24, 25–34, 35–44, 45–54, 55–64, 65–74 and 75 and older. Prescribed medications used by the sample were analysed only if the generic form of the medication was known. Patients not prescribed any medication served as the control group and all other medications were coded into categories based on known psychiatric and central nervous system (CNS) effects. Psychotropic medications were those classified as CNS medications in the Monthly Index of Medical Specialties (MIMS19) and are indicated for treatment of a psychiatric disorder, these included: antidepressants, antipsychotics, sedatives and agents for attentional-deficit hyperactivity disorder. Anticonvulsants were classed as psychotropic medications if the patient did not have a seizure disorder. ‘CNS-acting’ medications were defined as medications that are either: (a) classified in the MIMS CNS medication category but not primarily indicated for a psychiatric disorder or (b) not classified in the MIMS CNS medication category but can be prescribed as a psychiatric treatment or (c) not classified in the MIMS CNS medication category but have analgesic effects or significant CNS effects. Medications categorised as ‘other’ included medications with no or limited direct CNS effects and those not prescribed at all for psychiatric treatment. Medications that were not analysed in the models included medications most often used short term, agents used topically, vitamins and supplements. See online supplement DS1 for specific categorised medications.

Analysis

Data were analysed using SPSS for Windows 22.0. In analysis 1, unadjusted differences between the Alc− and Alc+ groups were assessed using logistic regression. Variables investigated included age, gender, whether the self-poisoning was premeditated (yes or no), year of presentation (1987–2014), medication prescribed (anticonvulsants, antidepressants, antipsychotics, sedatives, stimulants, CNS-acting, other and medication-free) and presence of any psychiatric diagnosis (yes or no). All explanatory variables were then included in multivariable logistic regression on the grounds of face validity. In analysis 2 logistic regression was used to compare odds ratios of Alc− and Alc+ across different psychotropic medication classes using medication-free as the reference category. Given the post hoc analysis of the HATS data, our non-directional hypotheses and large sample size, conservative Ps <0.01 and 99% confidence intervals were used to assess significance in all analyses to avoid identifying spurious associations that may be without clinical significance.

Results

Analysis 1

Figure 1 shows the flow diagram for inclusion. In total, 7270 patient records were included in analysis 1 (2907 men, 4363 women), aged 18–96. Thirteen (0.2%) patients died in hospital. At time of presentation, 1841 (25.3%) participants were in full- or part-time work, 1493 (20.5%) were unemployed, 1286 (17.7%) were receiving a pension, 476 (6.5%) performed duties at home, 329 (4.5%) were studying, 95 (1.3%) were retired and 62 (0.9%) were classified as ‘other’. The remaining 1688 (23.2%) had missing data for employment status. The majority of participants were single (n = 3397, 46.8%), followed by married (n = 2272, 31.3%), separated (n = 633, 8.7%), divorced (n = 538, 7.4%), widowed (n = 207, 2.8%), de facto (n = 31, 0.4%) or other (n = 6, 0.1%). The remaining 186 individuals (2.6%) had missing marital status data. A total of 2634 of the patients (36.2%) had co-ingested alcohol; an alcohol dose was reported for 1266 (17.4%), ranging from 1 to 30 standard drinks (median 7). Differences between Alc− and Alc+, age, gender, presentation year, presence of psychiatric diagnosis and prescribed medications are shown in Table 1.

Results from the bivariate analysis are also shown in Table 1. Analysis revealed the likelihood of Alc+ increased with presentation year. Compared with patients aged 18–24, those aged 45–54 had the highest odds of Alc+ and those aged over 75 had the lowest. Compared with men, women had a lower likelihood of Alc+. A higher likelihood of Alc+ was observed in those with any psychiatric diagnosis and those whose self-poisoning was unplanned. Odds of Alc+ were increased by 27% in medication-free patients and decreased 31% in those prescribed anticonvulsants, 45% in those prescribed antipsychotics, 13% in those prescribed antidepressants and 17% in those prescribed CNS-acting medications.
The results from the multivariable analysis are presented in online Table DS1. Age group, presentation year, female gender and unplanned self-poisoning remained significant. Use of antipsychotics remained lower in Alc+ presentations, as did CNS-acting medications. The multivariable analysis was rerun excluding planned self-poisoning (because of missing data for this variable) and results remained stable, except for use for antidepressants, which then became significantly lower in Alc+. The results from the bivariate analysis are shown in Table 2. The results from the multivariable analysis are presented in Table 1. Age group, presentation year, female gender and unplanned self-poisoning remained significant. Use of antipsychotics remained lower in Alc+ presentations, as did CNS-acting medications. The multivariable analysis was rerun excluding planned self-poisoning (because of missing data for this variable) and results remained stable, except for use for antidepressants, which then became significantly lower in Alc+ presentations (adjusted OR = 0.82, 99% CI 0.70–0.97, P < 0.001).

### Analysis 2

There were 3773 patients who were medication-free or using one psychotropic agent at time of presentation (1584 men, 2189 women) and 1490 patients (39.5%) had co-ingested alcohol. The results from the bivariate analysis are shown in Table 2. Compared with being medication-free, patients prescribed tricyclic antidepressants (TCAs) and typical antipsychotics had a reduced Alc+ odds.

### Discussion

To our knowledge this is the first study to investigate the relationship between prescribed psychotropic medications and co-ingested alcohol at time of self-poisoning. We identified clear differences in proportions of Alc+ between individuals prescribed different medications, both in the unadjusted and adjusted analyses. Our data drew multiple parallels to a US national cohort of 57,813 and 82,519 suicide decedents. Increased prevalence of men in Alc+ was evident in both aforementioned studies, as was age of peak Alc+ in the present study, which occurred between 35 and 54 years followed by a sharp decrease (Fig. 2). Overall rates of alcohol co-ingestion were slightly higher in our sample, although still reflect estimates that approximately a third of suicide attempts involve alcohol (36.2% in the present study v. 33.6%\(^5\)). This not only highlights the validity of the data, but also the similarities that exist between this largely non-fatal poisoning group with a sample of completed suicides. This supports a previous study using the HATS database that has shown that people who present to hospital for self-poisoning are at greatly increased risk of future completed suicide.\(^{17}\)

The novel findings of the present study were related to disparate proportions of Alc+ between people prescribed different medications. Importantly, these findings remained significant when controlling for known factors associated with heavy alcohol use and/or prescribing practices, such as male gender, age, presentation year, psychiatric diagnosis and the premeditated nature of the self-poisoning event. Bivariate analysis 1 showed that psychotropic use displayed significantly reduced odds of Alc+, and conversely that being medication-free was associated with increased odds. When adjusting for demographic and psychiatric variables, antipsychotics and CNS-acting medications maintained reduced odds of Alc+, whereas sedatives maintained reduced odds at trend level. Without the confounding influence of polypharmacy, analysis 2 allowed comparison across psychotropic classes. Compared with being medication-free, TCAs and typical antipsychotics conferred decreased odds of Alc+ by approximately 43% and 65%, respectively, and anticonvulsants conferred a trend-level decrease of approximately 52%. It is important to note that TCAs and typical antipsychotics share first-line treatment indications with agents that did not confer such marked reduced odds (i.e. other antidepressants or atypical antipsychotics), hence
the differences we see between these agents is not likely to be reflective of underlying psychiatric diagnoses.

Possible explanations for our findings

Given the wide range of significant results found across demographic, psychiatric and medication variables, there are multiple ways to interpret these data. We propose three separate, but not necessarily mutually exclusive, theories: (a) the mechanism of action of CNS medications interferes with alcohol-related circuitry; (b) that Alc+ is a proxy for impulsivity, which differs between the drug classes; and (c) appropriately medicating people at risk of self-harm reduces the likelihood of ‘self-medicating’ with alcohol or turning towards alcohol in times of emotional instability. Our first proposal is related to the potential for direct effects of the prescribed medications on alcohol-related behaviours, as hypothesised. It is interesting that in bivariate analysis 1, medications that act through the CNS (both psychiatric and non-psychiatric) showed reduced odds of Alc+, whereas medications with limited or no action in the CNS (‘other’) were not associated with Alc+. In other words, medications that act on similar pathways to alcohol are associated with reduced Alc+ and conversely, medications that are not known to act on similar pathways are not. Supporting this further is bivariate analysis 1 and 2, whereby antipsychotics, as medications with strong inhibition of dopamine, conveyed the lowest odds ratios of Alc+. That antipsychotics may reduce reinforcement of alcohol has been posited previously as an avenue for treatment of AUDs.20 Notably, the reduced odds found here appear to be driven by

### Table 2 Bivariate analysis comparing odds ratios of alcohol co-ingestion (Alc+) across psychotropic medication classes

<table>
<thead>
<tr>
<th>Prescribed medicationsa</th>
<th>Alc– group (n = 2283)</th>
<th>Alc+ group (n = 1490)</th>
<th>OR (99% CI)b</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication-free</td>
<td>1131 (49.5)</td>
<td>766 (51.4)</td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>272 (11.9)</td>
<td>197 (13.2)</td>
<td>1.07 (0.82–1.40)</td>
<td>0.52</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>40 (1.8)</td>
<td>13 (8.7)</td>
<td>0.48 (0.21–1.10)</td>
<td>0.2</td>
</tr>
<tr>
<td>Selective noradrenaline reuptake inhibitors</td>
<td>132 (5.8)</td>
<td>83 (5.6)</td>
<td>0.93 (0.64–1.36)</td>
<td>0.62</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>160 (7.0)</td>
<td>62 (4.2)</td>
<td>0.57 (0.38–0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>27 (1.2)</td>
<td>14 (0.9)</td>
<td>0.77 (0.33–1.80)</td>
<td>0.42</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td>31 (1.4)</td>
<td>29 (1.9)</td>
<td>1.38 (0.70–2.72)</td>
<td>0.22</td>
</tr>
<tr>
<td>Typical antipsychotic</td>
<td>55 (2.4)</td>
<td>13 (0.9)</td>
<td>0.35 (0.16–0.78)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atypical antipsychotic</td>
<td>80 (3.5)</td>
<td>42 (2.8)</td>
<td>0.78 (0.47–1.29)</td>
<td>0.19</td>
</tr>
<tr>
<td>Lithium</td>
<td>10 (0.4)</td>
<td>3 (0.2)</td>
<td>0.44 (0.08–2.42)</td>
<td>0.22</td>
</tr>
<tr>
<td>Sedatives</td>
<td>336 (14.7)</td>
<td>267 (17.9)</td>
<td>1.17 (0.92–1.50)</td>
<td>0.09</td>
</tr>
<tr>
<td>Stimulants</td>
<td>9 (0.39)</td>
<td>1 (0.07)</td>
<td>0.16 (0.01–2.49)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Alc–, no alcohol co-ingestion.
a. Medication categories are mutually exclusive.
b. Adjusted odds ratio of Alc+.

### Fig. 2 Variation in self-poisoning admission frequency by age with respect to alcohol co-ingestion.

Number of self-poisoning admissions with (Alc+) and without (Alc–) alcohol as a co-ingestant v. age. Black line represents total self-poisonings (left y-axis). Dashed line represents the proportion of total self-poisonings that were Alc+ (right y-axis) per age. Y-values are averaged over 3 years, 1 year younger and 1 year older for every data point.
treatment with these agents does not show increased odds of Alc+ in intentional self-poisoning. Alternatively, being medication-free and having a psychiatric diagnosis independently showed increased odds of Alc+, highlighting a potential risk associated with avoiding pharmacological treatment. So although our analysis cannot provide definitive conclusions as to why these associations are observed, overall results suggest that choosing to medicate patients may prove to be beneficial in terms of limiting alcohol use and, although speculative at this stage, this may have downstream effects in terms of reducing suicidal behaviour. The option to medicate may be especially relevant to those who are self-identified heavy drinkers, although again, this is speculative at this stage. On the other hand, being medication-free in this sample is also likely to represent a portion of patients who do not seek help from medical professionals and therefore do not have access to appropriate medications. In which case the importance of mental health treatment-seeking is highlighted.

These results also provide support for current neuropsychopharmacological rationales towards identifying and trialling medications for patients with comorbid AUD and psychiatric disorders. That is, medications that target neurobiological pathways known to be implicated in both AUD and the psychiatric diagnosis may show positive effects in terms of alcohol consumption as well as psychiatric symptoms. That said, clinical trials so far have not been promising, with no measured reduction in alcohol use observed from use of SSRIs or antipsychotics. This is an area that requires further research.

Strengths and limitations
This study has many strengths that include its large sample size and the complete capture by HATS of all patients admitted for poisoning in all the hospitals in greater Newcastle, therefore providing a good representation of individuals who are admitted to hospital for intentional self-poisoning in the area. The results of this study should be interpreted in the context of limitations. The proportion of fatal self-poisonings in the present study is small (0.2%), hence the results cannot be generalised to completed suicides or suicides that involve different methods. Many non-fatal self-poisonings do not present to hospital services, therefore this sample is an underrepresentation of total intentional self-poisonings. It is worth considering whether less-severe self-poisonings (and therefore less likely to present to HATS) involved more cases of Alc+, or fewer. Or conversely, whether fatal self-poisonings that do not reach hospital involve more cases of Alc+. Dose of alcohol was poorly populated in the data-set. Only 17% of the Alc+ group records had alcohol dose reported and the doses that were available varied substantially, from 1 up to 30 standard drinks, showing highly variable alcohol-related behaviours. The available data limit our potential to look at dose as a covariate, representing a significant limitation. Furthermore, the timing and intention of alcohol consumption is unknown, hence it is impossible to determine how many patients used alcohol as one of the agents to self-poison v. those who consumed alcohol prior to the self-harm. Although if alcohol was used solely as a co-ingestant to self-poison, we would not expect to see such large differences between prescribed medications, furthermore, that unplanned self-poisonings were higher in Alc+ indicates that in a proportion of included patients, alcohol was a proximal risk factor for self-poisoning. We had data recorded on poisoning intent (i.e. planned or unplanned) for 71% of our cohort that was most commonly collected on a pre-formatted toxicology admission chart. Missing data for this variable was most likely related to the significantly greater levels of unconsciousness/confusion that was recorded for these patients at presentation. Hence the adjusted odds ratios for analysis 1 is
skewed toward a sample with less severe neurological symptoms as a result of their poisoning, which may limit the generalisability of these findings.

Implications
We have presented three theories to describe the results of this study – first, that alcohol-related behaviours are inhibited by medications that act on the CNS; second, that Alc+ is either inducing impulsivity or acting as a proxy for it; and third, that non-medicated people at risk of self-harm may be more likely to self-medicate with alcohol. The relationship between alcohol and self-harm is complex and not able to be disentangled with a single proposal, hence we suggest the complex findings revealed here are likely to be a result of multiple influencing factors – with prescribed medications being the most modifiable of those. Overall, the findings suggest that providing appropriate medication for people with a psychiatric diagnosis is important for reducing the likelihood of Alc+, and perhaps by extension also reducing the risk of impulsive suicides.

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