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## Interaction between antidepressants and alcohol -- signal amplification by multiple case reports

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## **Abstract**

**BACKGROUND:** Alcohol use and antidepressant prescription are prevalent in many countries, but little is known about their combined effects.

**OBJECTIVE:** Having been surprised by selective serotonin reuptake inhibitor (SSRI) antidepressant-treated patients who became prone to pathological intoxication, we examined this association, searching for relevant literature and cases.

**METHODS:** A detailed literature search showed little or no interaction between SSRIs and alcohol in laboratory studies, and inconsistent effects of these drugs in problem drinkers. We collected cases to study from our own and colleagues' practices, regulatory agencies and web-based discussion fora, and considered evidence for interactions according to standard criteria.

**RESULTS:** Pathological intoxication, characterized by unexpected and often gross disinhibition, was identified in 100 of 201 reports that provided enough detail to be evaluated. Memory impairment was prominent in just over half (53/100) of these. Outcomes included serious violence; homicide occurred in 8 cases, including two double and one triple homicide.

**CONCLUSIONS:** Multiple lines of evidence amplify a thus far barely recognized signal of interactions of SSRI and related antidepressants with alcohol. Systematic collection of further data is required to further characterize this syndrome, but in the meantime effective warnings must be introduced to alert prescribers and patients to the serious risk of pathological intoxication during antidepressant treatment.

## **Keywords**

Alcohol; Antidepressant; Interaction; SSRI; Intoxication; Disinhibition; Violence

## Background

Antidepressants can cause complex behavioural effects, especially early in treatment, and after increase or decrease in dosage [1]. Alcohol also produces a range of psychological and behavioural effects, depending on the individual and the setting; people with mood disorder commonly use it [2]. Likewise depression is recognized as a frequent and sometimes serious complication of alcohol abuse [3].

Interactions between selective serotonin reuptake inhibitors (SSRIs, the most commonly used class of antidepressants) and alcohol have been studied in healthy volunteers, mainly in experiments measuring intoxication and psychomotor performance. In such settings, SSRIs tend not to impair function nor do they aggravate the effects of alcohol [4, 5]. Clinical trials have also studied the effects of antidepressants in problem drinkers, with and without co-morbid depression or anxiety. Though some people seem to benefit, the results are unimpressive overall [6]; a recent study of paroxetine in anxious drinkers, for example, shows unchanged overall risky drinking despite reductions in anxiety, and of drinking to cope with anxiety [7]. Similar results have been found with venlafaxine [8]. Clinical subgroups may be important since SSRI treatment appears to *worsen* drinking outcomes in type 2 (early onset, typically male, with positive family history) alcoholism [9, 10]. This finding has attracted little attention, and individuals so affected have been little studied.

In our work we have repeatedly met cases in which patients using an SSRI or related antidepressant took alcohol in usual amounts, and then behaved in

unexpected and uncharacteristic ways. Other patients known to us have substantially increased their alcohol intake during antidepressant treatment, sometimes with serious untoward effects. Such interactions have scarcely been recognized in the professional literature, with our conference abstract [11], several case reports [12-14], and a case series indicating emergence of alcohol dependence with SSRIs [15]. SSRI patient information leaflets do however warn users to avoid alcohol – without explaining why [16]. Similarly, US [17] and UK [18] government publications warn against combining alcohol and antidepressants, mainly because of the sedative potential of the older tricyclic drugs, but do not mention disturbed behaviour nor otherwise refer to SSRIs.

## **Methods**

A detailed literature search across 5 academic databases (see supplementary file #1) failed to identify additional reports of adverse behavioural effects of antidepressants combined with alcohol. Accordingly, we searched for and evaluated case reports from five available sources:

- Our combined practices included 39 people assessed to have psychological or behavioural disturbance associated with drinking alcohol during antidepressant treatment (criteria set out below). We included individuals whose alcohol intake changed significantly, either in amount or pattern, during antidepressant treatment.
- We similarly analyzed a colleague's case (n=1) and official pharmacovigilance reports (n=40) from the UK (MHRA) and USA (FDA).
- We studied several hundred of approximately 5000 case histories submitted between 1998 and 2007 by contributors to a web-based discussion of

antidepressant treatment experiences (originally posted to The Antidepressant Web at [www.socialaudit.org.uk](http://www.socialaudit.org.uk); regrettably this website is no longer maintained). Searches using the key words “alcohol” and “drinking” detected 49 distinct discussion threads that returned positive hits; 17 contained relevant cases (n=121) with enough detail to be analyzed; the two authors independently assessed the likelihood of a reliable antidepressant-alcohol interaction in each. Many reports included an email contact address; we asked 14 people (11.5%) for further information, or to clarify key points (see below).

- One case in the popular literature was described in sufficient detail to be included [19].
- Finally, we screened several hundred of 4800 archived media stories about adverse effects of SSRI treatment ([www.ssristories.com](http://www.ssristories.com)), but none of the stories were detailed enough to be assessed reliably according to our criteria (see below).

Assessment of reports from each source focused on: dosage and timing of the antidepressant and of alcohol; the description of associated psychological or behavioural disturbance; the context in which the disturbance occurred; and the outcomes. Other details in the reports, e.g., psychiatric or medical co-morbidity, were screened for possible relevance. We also looked for hints of bias by considering possible motivations (forensic, personal, political) of those presenting the case histories, and excluded several where bias seemed likely.

For each report, we considered the following coding categories for the possible interaction of alcohol with the antidepressant:

1. **exaggerated alcohol intoxication** (dose/response curve clearly shifted to the left)
2. **pathological alcohol intoxication**, for example with qualitatively different or uncharacteristic disinhibition or violence
3. **increased use of alcohol** (decreased use was noted in several cases and coded as 'minus 3')
4. **changed patterns of alcohol intake**, for example the emergence of daily drinking in someone with a history of drinking only at weekends
5. **memory impairment** (clearly beyond that expected from the amount of alcohol consumed)
6. **increased after-effects of alcohol**: hangover (several people also reported less hangover, coded as 'minus 6'); mood change; physical self-harm

We used standard WHO causality assessment criteria [20] for possible interactions in each report. Only reports with positive findings (probable or definite causality) in Categories 1 or 2 were considered 'cases', followed by a careful search for associated findings (Categories 3-6) and evidence of co-morbidity, either mental or physical. Both authors independently rated each report; disagreements in approximately one-sixth were resolved by discussion and consensus. In 14 reports, we obtained follow-up information from the subject by phone or email.

## **Results and discussion**

201 reports (listed in supplementary file #2) contained sufficient detail for evaluation; of these, a distinct syndrome of exaggerated intoxication or uncharacteristic disinhibition with alcohol was detected in 100 people of either sex

during use of an antidepressant; ‘caseness’ required probable or definite findings in Categories 1 or 2 (see Method) [20]. Outcomes included homicide (8 cases, including two double and one triple, i.e. 12 deaths), attempted murder, attempted and completed suicide, and many cases of serious assault, unintended sexual intercourse, and other damaging or painfully embarrassing social behaviour. A typology of cases (Table 1) showed two distinct response groupings across antidepressants; in roughly half (53/100) of cases, memory for the index episode was lacking, often completely. A comparable pattern of results emerged from each of our three sources of data, from reports originating in different countries, and was broadly similar across various SSRIs, venlafaxine, and bupropion (Table 1; see also tables in supplementary file #2).

A striking finding was that most cases of exaggerated or pathological intoxication (Categories 1 and 2) involved only modest or usual amounts of alcohol, with evidence that these had been well tolerated before antidepressant treatment, and after its discontinuation (challenge-dechallenge). In at least four cases, re-exposure to the same or a related antidepressant reproduced the phenomenon (rechallenge). In addition, one-third (32/100) of cases gave a clear history of increased drinking or a distinctly altered pattern of alcohol use during antidepressant treatment (Table 1). A similar proportion of screened individuals lacking evidence of pathological intoxication (‘non-cases’) also reported such a change in alcohol consumption while taking an antidepressant (supplementary file #2); in several instances there was good evidence of causation: increased drinking remitted when antidepressant use ceased, and recurred on its resumption (challenge-dechallenge-rechallenge).

Anonymised examples (Table 2) illustrate characteristic response patterns.

Since the welcome rise of evidence-based medicine in the 1980s, case series are widely thought to provide much weaker evidence than controlled trials, case-control or cohort studies. This view is justified for evaluations of effectiveness, but not for the evaluation of harms, for which the hierarchy of evidence is reversed [21, 22]. The majority of adverse effects first come to light in case reports and case series [23], not in clinical trials or other prospective or epidemiological work. Case series are followed by specific studies to investigate and explain how they happen, how they might be prevented or harms minimized. Our search revealed only case reports, more impressive in numbers than in detail, and they required extensive analysis before patterns could be discerned.

## **Conclusions**

Our findings delineate a syndrome of pathological alcohol intoxication in patients treated with antidepressants. Available data do not allow an estimate of prevalence, but the number of reports suggests that the problem is not rare and occurs in a broadly similar manner across SSRIs and related drugs. Whilst confidence in causality varied across reports, some included sufficient detail to establish definite 'caseness', based on standard (challenge/ dechallenge/ rechallenge) criteria [20].

Memory impairment for index episodes of pathological intoxication is a distinctive feature in just over half (53/100) of our cases. This is forensically relevant and a source of psychosocial disturbance and personal embarrassment for many. Violence or sexual indiscretions played a role in many narratives that ended in a broken relationship. Impaired memory may also help to explain the apparent loss of self-

metering of alcohol intake noted in some of these cases, including one published as a case report [12].

Our study is limited by the opportunistic collection of cases, use of historical data derived largely from cross-sectional self-reports, some with missing demographic detail, and the apparent motivations (personal, forensic, or political) in some narratives. We tried to control for these possible distortions in our systematic causality assessment, as described, and took care to avoid leading questions in our interviews and email communications with potential cases.

Aggregated pharmacovigilance data (in preparation) corroborate the existence of major interactions between alcohol and SSRIs that neither manufacturers nor regulators have properly recognized. The MHRA, for instance, on its website lists 129 reports categorized as interactions of SSRIs and related drugs with alcohol – but seems not to have examined them collectively, perhaps because the Yellow Card database is organized by drug name, not by pharmacotherapeutic group. As a result the relationships between drugs are not visible [24]. Regulators thus function as ‘aggregate-keepers’ who here recognise the trees but not the wood.

Systematic and detailed examination of cases is necessary to understand the various ways in which alcohol and antidepressants can interact. Estimates of frequency will require prospective studies, given the well recognised under-reporting of adverse drug reactions -- and the likelihood that interactions are even less well recognized or reported. This may be particularly true of interactions with alcohol [17], which both patients and professionals tend to keep in a separate conceptual box.

As we have detailed elsewhere [16], existing antidepressant product warnings about alcohol are non-specific and quite unhelpful. Partly for this reason, people prescribed antidepressants generally ignore warnings to avoid alcohol. We suggest that package inserts and summaries of product characteristics be urgently revised and well tested on users to ensure that they adequately warn both prescribers and consumers of this potential interaction. This may also improve detection and facilitate study of the problem.

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### **Supplementary files**

Supplementary file #1 summarizes the results of literature searches conducted October 2011 and June 2014.

Supplementary file #2 contains two Excel spreadsheets, one with case details, the second with tabulated summaries of the results, broken down by data source.

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**Table 1. Typology of cases with sufficient detail to be analyzed**

<b>Drug &amp; approximate year of UK introduction</b>	<b>reports</b>	<b>cases</b>	<b>memory loss</b>	<b>increased alcohol use</b>	<b>serious violence</b>	<b>males</b>
bupropion (1999)	1	1	1	0	1	1
citalopram (1997)	16	4	2	0	0	0
desvenlafaxine*	1	1	1	0	0	0
escitalopram (2002)	4	0	0	0	0	0
fluoxetine (1984)	54	28	17	8	16	10
fluvoxamine (1980)	1	1	0	0	1	1
paroxetine (1990)	97	51	23	19	26	22
sertraline (1990)	5	4	3	3	4	2
venlafaxine (1991)	22	10	6	2	8	6
<b>All</b>	<b>201</b>	<b>100</b>	<b>53</b>	<b>32</b>	<b>56</b>	<b>42</b>

Table 1 legend. Cases are reports with probable or definite pathological intoxication, as described in Method. The last four columns indicate frequencies among defined cases for each drug. Serious violence includes homicide, attempted murder, suicide, significant self-harm, and assault leading to hospitalization of the victim or a criminal charge. \* not registered in the UK.

**Table 2. Summary of illustrative cases**

<i>Case and country of origin</i>	<i>Source</i>	<i>Sex</i>	<i>Age</i>	<i>Drug</i>	<i>Description</i>
1	ADW	F	35	paroxetine	Uncharacteristic verbal and physical aggression after 2-3 drinks, remitted when discontinued and recurred when resumed paroxetine (CDR). Seriously injured, lost teeth during one episode; relationships jeopardized; lost boyfriend.
2	ADW	F	?	fluoxetine	No problem until started drinking; craved alcohol "all the time" and became disinhibited with impaired judgment, regrettable loss of virginity. Experienced blackouts, told of further "stupidity" by friends; very embarrassed. Clear history of remission of pathological alcohol effect and recurrence when stopped and later re-started drug (CDR).
3 UK	ADW	F	?	paroxetine	Treatment effective for mood and bulimia symptoms, but noted exaggerated effect, "passing out" on previously well tolerated amounts of alcohol. Increased dose (20 mg/d) resulted in craving, blackouts, and "crazy" behaviour. Arrested twice. Clear history of dose dependence, and of CDR when stopped and resumed paroxetine.
4	ADW	M	?	paroxetine	Took drug for 2 months on two occasions; during both he noticed an exaggerated sensitivity to alcohol, "...requires only a small quantity to achieve inebriation... very easy to lose control". Complete resolution when drug discontinued.
5 UK	AH	M	25	paroxetine	Young man with social anxiety and history of heavy drinking noticed dramatic increase in sensitivity to alcohol during paroxetine treatment, becoming "grossly intoxicated on just 2 cans of beer", falling over, getting lost.
6 UK	AH	M	31	venlafaxine	Man with anxiety and depression tolerated but did not respond to sertraline. When switched to venlafaxine, 150mg/d, he became intoxicated on one glass of wine, drove erratically, failed to stop, resisted arrest, and was violent with police. He had no memory of these events and faced criminal charges.
7 UK	AH	M	36	bupropion	A police dog handler with no prior history of violence was prescribed bupropion (150 mg/d) to aid smoking cessation. During dinner with his wife he drank 11 units of alcohol over 4 hours and became inexplicably irritable and violent, punching her twice. He was charged with assault and resisting arrest, and suspended from work.
8 UK	MO	F	35	fluoxetine	Woman treated for anxiety and depression with fluoxetine; she found a recurrent, extremely distressing pattern of uncharacteristic disinhibition with usual modest amounts of alcohol, including multiple episodes of unintended sexual intercourse. The problem completely ceased when she stopped fluoxetine.
9 USA	DM	M	40	fluoxetine	Upset at relationship loss, this sleep-deprived man took an initial 40-60mg dose of fluoxetine and over 5 hours drank 200-300 mL of whisky before driving across town and shooting his ex-partner and two others to death. He had no prior history of violence and now faces life imprisonment.
10 UK	DM	M	28	paroxetine	Treated for depression, this man noted emotional detachment more than a lift in mood. Previously a weekend drinker, on paroxetine he developed a craving for alcohol, and began drinking 4-5 cans of beer daily, which made him irritable and sullen. He fatally stabbed a neighbour with a pocketknife during a public altercation and has scant memory of the event.
11 USA	PV	F	?	fluoxetine	Report of woman taking fluoxetine who consumed 3 drinks and shot and paralyzed her boyfriend before attempting suicide. She had no prior history of violence, and was convicted of attempted murder.
12 USA	PV	F	24	paroxetine	Woman treated with paroxetine got uncharacteristically and repeatedly drunk, arrested for speeding, running red lights and killing another driver. Convicted of manslaughter. On another occasion hit a policeman.
13 USA	PV	M	16	paroxetine	Never before aggressive or violent, this boy was prescribed paroxetine, but didn't like it because he felt "jittery and weird". Parents noted he became increasingly aggressive. After 3 weeks of treatment, he robbed his step-grandmother and stabbed her 61 times after drinking alcohol; convicted of homicide.

Table 2 legend. Case sources included the Antidepressant Web discussion forum (ADW), cases personally assessed by the authors or a colleague (AH, DM, MO), and three from the US Food and Drug Administration pharmacovigilance databases (PV). Countries of origin indicated in column one; those unspecified are unknown. Case 7 has been reported separately (ref. 13).