

# Intravenous ethanol for alcohol withdrawal syndrome in intensive care units

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## Abstract

### Introduction

Although not often recommended, ethanol replacement is still used in hospitals, including ours. Since intravenous ethanol for alcohol withdrawal is mainly used in the intensive care units of our clinic, we reviewed literature to enable better liaison psychiatric consult for patients in this particular setting.

### Materials and methods

We performed a MEDLINE search for pharmacological trials with alcohol dependent patients in intensive care units who were treated with, or who received intravenous ethanol as prophylaxis for alcohol withdrawal syndrome. Efficacy, eventual referral to addiction aid and post-interventional abstinence were chosen as outcome measures. If a withheld review article mentioned the search strategy, the search was carried forward from their end-date till ours in order to detect more recently published papers. In parallel, we initiated a small retrospective evaluation of our hospital's electronic patient-records mentioning 96% ethanol 10ML ampoules.

### Results

Retrospective analysis: Preliminary results indicate a rather anecdotic use of intravenous ethanol in our university hospital to prevent or treat alcohol withdrawal syndrome. Literature search: After our initial

search, reference tracking and reproducing searches of relevant systematic reviews we identified 8 interventional trials. Those indicate, in accordance with recent systematic reviews, that intravenous ethanol is not more efficient than active control to prevent alcohol withdrawal syndrome. Numbers of referral to addiction aid and abstinence after discharge of patients was either unknown or low.

### Discussion

Intravenous ethanol is not more efficient than active control to prevent alcohol withdrawal syndrome. Several reservations concerning methodology of trials on IVetOH use have been addressed. Consideration of a more unified study population (elective surgery vs. medical and trauma ICU patients) could be necessary. Ethical reflections and possible harm are also discussed.

### Conclusion

In the selected interventional trials, intravenous ethanol was not superior to active control in preventing alcohol withdrawal syndrome. Furthermore, intravenous alcohol replacement is not advised due to its potential harm.

### Introduction

Several recent review articles and guidelines have spoken out against<sup>1,2</sup> or even stopped addressing<sup>3,4</sup> the use of ethanol replacement for the prevention or treatment of alcohol withdrawal syndrome (AWS). Yet, we sporadically witnessed the use of intravenous ethanol (IVetOH) in hospitals, including ours.

A decade ago this practice was prevailing in more than half of US Teaching Hospitals<sup>5</sup> and 15 of the 96 Dutch ICU's responding to a questionnaire in 2000 equally confirmed ethanol application<sup>6</sup>.

Further query at the academic central pharmacy revealed that 96% ethanol 10ML ampoule IV is still in our formularies. The largest proportion is used in intensive care units (ICU) and the operating ward. Hence, we commenced a sample in-hospital retrospective analysis. Meanwhile, we reviewed clinical trials of alcohol dependent ICU patients receiving IVetOH, to evaluate efficacy in AWS prevention or treatment.

We also examined if, and how, addiction treatment for the actual dependency was organized for the IVetOH-administered patients. This, hopefully, will improve our liaison psychiatric advice when consulted by intensive care workers facing alcohol dependent patients.

### Materials and methods

#### Search strategy

We conducted a MEDLINE search to identify studies published up to 28 February 2014. Emphasis was on interventional trials with intravenous ethanol as treatment or prevention of AWS for ICU alcohol dependent patients. Publications on surgical and/or critically ill patients could be included since they are likely to be transferred to ICU. We combined subject indexing terms and free text words as search terms. No language or time restrictions were used. Table 1 shows the full electronic MEDLINE search strategy, co-designed by our head librarian. We also searched the same database with the keywords delirium and guideline (free text). We hand-searched the reference lists of the included publications to identify additional articles of interest.

Finally, when specified, we reapplied the MEDLINE search strategies from relevant systematic reviews from their end-date until 28 February 2014.

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**Table 1: the full electronic MEDLINE search strategy.**

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((((((((("adult"[MeSH Terms] OR "adult"[All Fields]) OR ("aged"[MeSH Terms] OR "aged"[All Fields]) AND ("critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields]) OR ("intensive care units"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields] AND "units"[All Fields]) OR "intensive care units"[All Fields]) AND ("treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields]) AND "alcohol withdrawal delirium/drug therapy"[Mesh Terms] OR (("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) AND Withdrawal[All Fields]) AND ("injections, intravenous"[MeSH Terms] OR ("injections"[All Fields] AND "intravenous"[All Fields]) OR "intravenous injections"[All Fields] OR ("injections"[All Fields] AND "intravenous"[All Fields]) OR "injections, intravenous"[All Fields]) AND "delirium/prevention and control"[Mesh Terms] AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "control"[All Fields] OR "control groups"[MeSH Terms] OR ("control"[All Fields] AND "groups"[All Fields]) OR "control groups"[All Fields]) AND ethanol*[All Fields] AND ("organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "administration"[All Fields]) AND dosage[All Fields] OR (("ethanol"[MeSH Terms] OR "ethanol"[All Fields]) OR ethanol*[All Fields]) AND ("therapeutic use"[Subheading] OR "therapeutic"[All Fields] OR "therapeutic use"[All Fields])) AND (intravenous[All Fields] AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields])) OR (IV[All Fields] AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields])) OR (("ethanol"[MeSH Terms] OR "ethanol"[All Fields] AND infusion[All Fields]) AND (hasabstract[text] AND "humans"[MeSH Terms]) NOT ablation[All Fields] NOT ("infection"[MeSH Terms] OR "infection"[All Fields]) NOT ("embolization, therapeutic"[MeSH Terms] OR ("embolization"[All Fields] AND "therapeutic"[All Fields]) OR "therapeutic embolization"[All Fields] OR "embolisation"[All Fields]) NOT ("oxidoreductases"[MeSH Terms] OR "oxidoreductases"[All Fields] OR "dehydrogenase"[All Fields])) NOT ("methanol"[MeSH Terms] OR "methanol"[All Fields]) NOT ("in vitro"[Publication Type] OR "in vitro"[All Fields]) NOT ("laboratories"[MeSH Terms] OR "laboratories"[All Fields] OR "laboratory"[All Fields]) NOT ("healthy volunteers"[MeSH Terms] OR ("healthy"[All Fields] AND "volunteers"[All Fields]) OR "healthy volunteers"[All Fields]) NOT ("sclerotherapy"[MeSH Terms] OR "sclerotherapy"[All Fields])) NOT ("infant"[MeSH Terms] OR "infant"[All Fields])))

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### Selection of studies

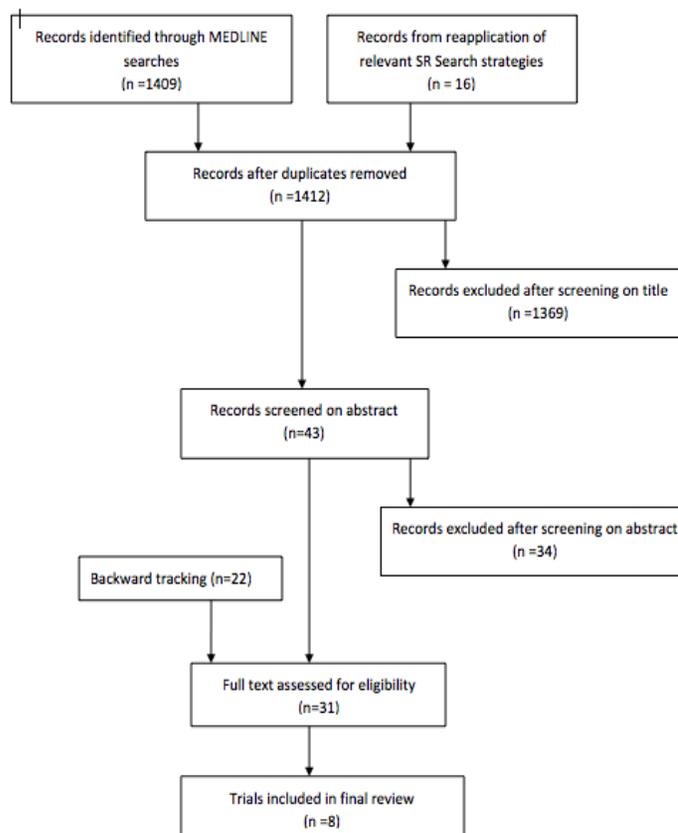
Two reviewers independently screened title and abstract, disagreements were resolved by discussion and then full texts were evaluated. We included all papers on adult alcohol dependent patients for whom IVetOH was administered to prevent or manage AWS (including delirium tremens) in ICU. We excluded papers not clearly concerning ICU-patients and trials where IVetOH was combined with oral alcohol.

### Quality appraisal

All publications that contained original research data were evaluated for methodological quality using the checklist based on the methodology prescribed by the Scottish Intercollegiate Guidelines Network (SIGN)<sup>7</sup>, cfr supplement 1: Levels of evidence grading via SIGN. Taking into account the limited number of available trials, only levels of evidence equal or less than 4 were excluded after content and reference review.

### Retrospective study of electronic patient-records mentioning 96% ethanol 10ML ampoules

To ensure that 96% ethanol 10ML ampoules IV were actually diluted in

**Figure 1:** The flow-diagram of the study-selection process.

an intravenous infusion and used as prophylactic or treatment of AWS we started examining patient records from august 2003 until august 2013

mentioning the 96% ethanol 10ML ampoule IV. This was approved by the ethical committee of our University hospital (UZ Brussel).

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## Results

### Retrospective study of electronic patient-records mentioning 96% ethanol 10ML ampoules, preliminary results

Over a 10 year period, 166 electronic patient-records mentioned 96% ethanol. In the 50 files we were able to verify up till now, it was used 44 times for AWS. Further examination is still needed to evaluate efficacy, patient demographics, referral to addiction aid and is also necessary to differentiate preventive from therapeutic use. We will await involvement of our statistics department before continuation.

### Search results

The MEDLINE searches (Table 1) identified 1409 studies, of which 42 were eligible based on the title. After abstract screening and backtracking, 31 full texts were assessed. 8 trials met all eligibility criteria and were subject of further quality appraisal. Reproducing specified MEDLINE search strategies of retrieved systematic reviews (SR) revealed one extra publication (SR<sup>8</sup>: 3 more recent relevant articles were published since, of which one wasn't retrieved through our initial search. SR<sup>9</sup>: 13 more recent relevant articles were published since, all were already obtained through our initial search.). The flow-diagram of the study selection process is presented in figure 1.

There are 2 comprehensive systematic reviews (mentioned above) regarding the management of AWS but no guidelines specifically for the target group of ICU patients. The 8 retained trials<sup>10,11,12,13,14,15,16,17</sup> are described and graded in table 3 and further discussed below.

Overall, the trials had small patient samples, used various definitions of alcohol dependency (cfr. table 4), AWS and other variables. There were great differences in IVetOH concentration and titration (or use of a fixed schedule). A potential confounding or attribution bias might be linked to studies with only elective surgery ICU

Table 2: Levels of evidence grading according to SIGN.

#### LEVELS OF EVIDENCE

- 1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
- 1+ Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
- 1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias
- 2++ High quality systematic reviews of case control or cohort studies
- High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2+ Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non-analytical studies, e.g. case reports, case series
- 4 Expert opinion

patients versus those with trauma and critically ill ICU patients (cfr. discussion section).

All 8 ICU trials evaluated IVetOH used in prevention of AWS; none studied it as a treatment. Earlier research often confounded both; as adequately addressed in<sup>8,9</sup>. In accordance with their conclusions, and a 2004 review<sup>18</sup> efficacy of prophylaxis with IVetOH is not sufficiently proven despite since published investigation of<sup>12</sup> or a comparative trial with diazepam by<sup>11</sup>. Additionally we point out that, in all the IVetOH research in ICU, numbers of referral to addiction aid and abstinence after discharge of patients was either unknown or low (cfr. Table 3).

### Discussion

Delirium tremens (DT) has a high prevalence in the ICU; and 60% to 80% patients in the medical ICU suffer from delirium in general. This is in part attributable to age, severe somatic illness or post-operative state of the patient and in part due to the particularities of his surroundings. The latest holds a number of difficult to avoid risk factors for delirium: use of intravenous lines, sleep deprivation and many others<sup>19</sup>.

Controlling certain risks for delirium, such as pain, anxiety or insomnia, with sedative and analgesic medication poses a risk factor in itself. So does tapering them off too quickly.

A differential diagnose between deliriums in general, and DT or even AWS is hard to make in such environment, certainly not when the patient is intubated or otherwise unable to participate in a mental examination. In view of the difficulty to differentiate DT from delirium by other causes, the Dutch Delirium guideline<sup>3</sup> recommends first starting haloperidol in delirium patients with somatic illness, adding benzodiazepines in case of aggravating or confirmed withdrawal delirium. Most guidelines propagate benzodiazepines as first line medication for all DT, indiscriminative of concurrent physical illness or not<sup>1,2</sup>.

In most psychiatric and some general wards the CIWA-Ar (revised Clinical Institute Withdrawal Assessment for Alcohol) has become the standard diagnostic tool for AWS. Thanks to its assessment of AWS severity, it also forms guidance in symptom-triggered benzodiazepine substitution and evaluates the necessity for transfer to the ICU. This could be one reason for the 10% to 33% of ICU patients with alcohol use disorders (AUD), along with a higher risk for trauma and violence when alcohol intoxicated and alcohol-related chronic medical complications. The number of AUDs is even higher in academic ICUs<sup>20</sup>. Nevertheless, as mentioned above, CIWA-Ar is difficult to use in non-responsive ICU patients. The recently validated "Prediction of Alcohol Withdrawal Severity Scale" (PAWSS) might help prevent AWS progression in the hospitalized medically ill<sup>21</sup>.

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**Table 3: Description of trials with IVetOH for AWS Legend to Table 4 GER: Germany US: United States n: number of patients in IVetOH group, CIWA-Ar: revised Clinical Institute Withdrawal Assessment for Alcohol scale, Riker scale: Sedation -Agitation Scale as described by Riker, CG: control group, BAL: blood alcohol level, LoE: Level of Evidence (cfr SIGN) flu: flunitrazepam clon: clonidine, cmz: chlometiazole, hp: haloperidol, DT delirium tremens, LOS: Length of stay , BAL: blood alcohol level, g: gram, kg: kilogram, d:day, vs. versus, h: hour +Psy: one of the authors is a psychiatrist.**

Study (Country)	Department affiliation (first, last and/or corresponding author) Involvement of any author of Psychiatry:	LoE Design	n	IVetOH Intervention	Outcome & findings	Tapering	Psy-consult or referral offered	Post-interventional abstinence
Eggers et al. <sup>10</sup> 2002 (GER)	Anesthesiology Intensive Care +Psy	LoE3 prospective, observational uncontrolled nonblinded	32	Bolus (based on anamnestic drinking pattern) followed by continuous infusion (titrated according CIWA-Ar) for 1 to 9 days , in median 2	19 AWS prevented ( CIWA-Ar less than 20) -No suitable determination method for alcohol concentration in IVetOH treatment, titration based on clinical status preferred	No. after successful AWS prophylaxis, ethanol was continued by gastric tube	Not mentioned	Patients desiring abstinence were excluded
Weinberg et al. <sup>11</sup> 2008 (US)	Surgery No Psy	LoE1- prospective randomized controlled nonblinded  (vs. scheduled-dose diazepam for 24 patients)	26 (of 50)	Continuous infusion (titrated to maintain Riker score 4) for 4 or more days	25 AWS prevented (vs. all 24 with diazepam) -IVetOH offers no advantage in efficacy or sedation compared to diazepam , which gives better control of agitation	Yes, in 48 hours after 2 days (or any next day) if patient had a Riker score of 4 or less	20 consented to Brief Intervention of a social worker	yes
Dissanaike et al. <sup>12</sup> 2006 (US)	Surgery No Psy	LoE2-controlled (retrospective CG) nonrandomized	160* (68 protocol, 98* historical CG)  *unknown number of only oral alcohol	Protocol: continuous infusion (titrated to keep BAL below 0,08%) for a mean of 3 days  historical CG: physician preference, unclear how many were treated with oral alcohol	63 AWS prevented in protocol group -No significant morbidity from IVetOH (except 1 hyponatremia in protocol group) -Protocol: Shorter treatment (historical CG mean of 7 days) initiated sooner and more efficacy ( 93% prevented AWS vs 80% in historical CG developed AWS)	Yes, for protocol group. The rate was decreased to stop in 72 hours if no AWS after 1 day	Recommended in protocol, not always implemented. 14 referrals in protocol group, 7 in historical CG	yes
Spies et al. <sup>13</sup> 1995 (GER)	Anesthesiology Intensive Care No Psy	LoE 1- prospective randomized controlled nonblinded ( but CIWA-Ar rater was unaware of regimen)  vs. 48 flu-clon vs. 49 cmz-hp vs. 50 flu-hp	50 or 55 (of 197 or 220)	Bolus followed by continuous infusion (titrated according CIWA-Ar)	48? AWS prevented (55 pts initially on IVetOH, 2 were removed for DT and 3 after additional benzodiazepines intake. Of 50 pts remaining in study 2 had CIWA-Ar>20) -4 pharmacologic regimens had comparable AWS incidence, ICU LOS or complications (except tracheobronchitis elevated in cmz-hp)	Not mentioned	Not mentioned	Not mentioned

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Table 3: (continued)

Heil et al. <sup>14</sup> 1990 (GER)	Anesthesiology Intensive Care <i>No Psy</i>	LoE 2+ Prospective controlled nonblinded <i>scarce data (congress proceedings)</i> 9 of 19 patients without prophylaxis after randomization	10	Continuous infusion 2 to 4g/h	10 AWS prevented (vs. 6 AWS of 9 in control group)	Not mentioned	Not mentioned	Not mentioned
Huber et al. <sup>15</sup> 1990 (GER)	Surgery <i>No Psy</i>	LoE 2- prospective controlled nonblinded <i>scarce data (congress proceedings)</i> vs. clon 17 or 18? vs midazolam 17 or 18?	17 or 18? (Approximately: a third of 52)	Continuous infusion 1 to 2 g/kg/d	2 DT's and an unspecified number of seizures in IVetOH group -IVetOH is effective, although less than benzodiazepines -clonidine isn't an appropriate treatment	Not mentioned	Not mentioned	Not mentioned
Wilkens et al. <sup>16</sup> 1998 (GER)	Anesthesiology Intensive Care <i>No Psy</i>	LoE3 prospective uncontrolled	11	Bolus (calculated to obtain BAL 0,6g/L) followed by continuous infusion (titrated according CIWA-Ar) for 1 to 9 days, in median 2	10 AWS prevented, 1 patient with prodromal AWS and subsequent oral administration of ethanol	Mixed. -One patient: tapering but with simultaneous increased use via gastric tube. -One patient: Stop IVetOH and start clonidine. -Nine patients: not mentioned.	Not mentioned	Not mentioned
Hansbrough et al. <sup>17</sup> 1984 (US)	Surgery <i>No Psy</i>	LoE3 prospective uncontrolled	22	Continuous infusion (keeping BAL between 0,2 to 1,2mg/L) for 3 to 8 days	22 AWS prevented -infusion rates of 0,02 to 0,06g/kg per hour provide BAL of 2 to 8mg/ml at which no sedation or toxic effects were observed	Yes, over 24 to 36 hours	Not mentioned	Not mentioned

Once a patient suffers from severe AWS or DT, he is unable to collaborate in any medical decision on his behalf. He can't express the desire for abstinence nor the opposite.

Substituting with ethanol might not accord with the patient's wishes, for say when he was admitted after an unsupervised home attempt to abstain. In the same way, including patients in an interventional trial with IVetOH seems only possible in prevention studies, otherwise the patient's autonomy is compromised and such is not in line with the Helsinki Declaration.

On the other hand lays the responsibility to provide valid scientific results.

Ethical research<sup>22</sup> explored the in- or exclusion of elderly who lacked capacity but willingly took part in a delirium study (with agreement of their Local Research Ethics committee). Excluding those patients changed the outcome.

A selection bias in some of the 8 trials (cfr. Table 3 and Table 4) is assumable, when results of trials with elective surgery ICU patients are compared to those mixed with trauma and medically ill ICU patients.

Hypothetically, patients who were screened for alcohol dependence might have benefited from this. Since 'Answering research questions on drinking could alter subsequent (reported) behaviour in brief

intervention trials'<sup>23</sup>. Furthermore, informed consent implies understanding of symptom-triggered therapy, possibly this led to more valid scoring.

Finally, patients giving informed consent to alcohol substitution acknowledge their dependence, recognize it as a medical problem and might be more prone to change. Achieving abstinence during hospitalisation, independently of the reason of admission, seems evident to us. ICU could be a "teachable moment" concerning one's drinking habits. It has been shown that alcohol use decreased 3 months after ICU stay, and then increased after a year but not returning to baseline levels<sup>24</sup>.

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**Table 4: Alcohol Withdrawal Syndrome DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Third Edition text revised.**

Study (Country)	Consent by pt or proxy?	ICU admission Elective surgery (planned) vs. Trauma (and critically ill)	Dependence
Eggers et al. <sup>10</sup> 2002 (GER)	Only elective surgery pt consented. Next of kin consented if trauma. Pts stated not wanting abstinence (else exclusion)	AWS in 55 % trauma pt 17% elective surgery pts (Gastrointestinal tract) TRAUMA(20)>ELECTIVE(12)	DSM-IV criteria for alcohol dependency or consuming less than 60g of alcohol a day
Weinberg et al. <sup>11</sup> 2008 (US)	Pt consent	All trauma pts, expected admission of at least 4 days TRAUMA	chronic daily alcohol consumption of 5 or more US beverage equivalents for at least the last 6 months
Dissanaike et al. <sup>12</sup> 2006 (US)	No mention	Table 3, mainly trauma protocol: 'among surgical pt, both in ICU and the regular wards, continuing in the operating rooms' TRAUMA>ELECTIVE	daily alcohol use more than or equal to 2 drinks or more than 2 binge drinking episodes per week or history of AWS or current drinking with history of treatment for alcohol (related disease process)
Heil et al. <sup>14</sup> 1990 (GER)	No mention, But screened with Munich Alcoholism Test (MALT)	(neck tumour-resection, 19 dependent of 50 pts who had reported alcohol use) ELECTIVE	Daily intake of 145g or more and MALT score above 10
Huber et al. <sup>15</sup> 1990 (GER)		(52 alcohol dependent included from 218 oesophagusca pts) 48h post-op intubation by protocol ELECTIVE	daily intake at least 100g for last 2 year minimal daily
Spies et al. <sup>13</sup> 1995 (GER)		Consecutive pts undergoing resection of ca of the upper digestive tract ELECTIVE	DSM-III-R and daily intake at least 60g
Wilkens et al. <sup>16</sup> 1998 (GER)	Pt consent	ELECTIVE	'alcoholism' of at least 3 years and admitted dependence, daily intake from 50 to 900g (but unknown in 6 of 11)
Hansbrough et al. <sup>17</sup> 1984 (US)	No mention	TRAUMA (burn injury)	6-pack of beer = 4 ounces liquor or equivalent intake of wine per day

Rarely, detoxification is still delayed, postponed or even avoided by ethanol substitution with the idea that it helps patients to tolerate procedures<sup>25</sup>. Besides negative outcomes of not caring for their chronic illness, alcohol dependency, it also results in more post-operative complications than in those patients who withdrew from alcohol 1 month prior to surgery<sup>26</sup>.

### Conclusion

Intravenous ethanol is not more efficient than active control to prevent alcohol withdrawal syndrome. Beside several reservations expressed earlier

concerning methodology of trials on IVetOH use, considering a more unified study population (elective surgery vs. medical and trauma ICU patients) could be necessary. Low referral rates to addiction consultation and abstinence after intravenous administration of ethanol might be other reasons beside its non-superior efficacy and potential harm to avoid IVetOH as treatment as well as prophylactic.

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