A systematic review of the evidence for acute tolerance to alcohol – the “Mellanby effect”

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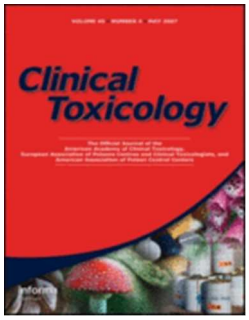

A Systematic Review of the Evidence for Acute Tolerance to Alcohol—the "Mellanby Effect"

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Abstract:	Abstract Objective: To review the evidence for 'the Mellanby effect,' that is, that the response to a given blood alcohol concentration (BAC) is more marked when BAC is rising than at the same concentration when BAC is falling. Methods: We systematically searched the databases EMBASE, Medline, and Scopus up to and including December 2016 using text words 'tolerance,' 'ascending,' 'descending' or 'Mellanby' with Medline term 'exp *alcohol/' or 'exp *drinking behavior/' or equivalent. Articles were identified for further examination by title or abstract; full text articles were retained for analysis if they dealt with acute (within dose) alcohol tolerance in human subjects and provided quantitative data on both the ascending and descending parts of the BAC–time curve. Reference lists of identified works were scanned for other potentially relevant material. We extracted and analyzed data on the subjective and objective assessment of alcohol effects. Results: We identified and screened 386 unique articles, of which 127 full-text articles were assessed; one provided no qualitative results, 62 involved no human study, 25 did not consider acute tolerance within dose, and 13 failed to provide data on both ascending and descending BAC. We extracted data from the 26 remaining articles. The studies were highly heterogeneous. Most were small, examining a total of 770 subjects, of whom 564 received alcohol and were analyzed in groups of median size 10 (range 5–38). Subjects were often young white men, sometimes subdivided on the basis of drinking or family history. Doses of alcohol and rates of administration differed. Performance was assessed by at least 26 different methods, some of which measured many variables. We examined only results of studies which compared results for a given alcohol concentration (C) measured on the ascending limb (Cup) and the descending limb (Cdown) of the BAC, whether in paired or parallel-group studies. When subjects were given alcohol in more than one session, we

	considered results from the first session only. Rating at Cdown was better than at Cup for some measures, as expected if the Mellanby effect were operating. For example, subjects rated themselves less intoxicated on the descending limb than at the same concentration on the ascending limb in 12/13 trials including 229 subjects that gave statistically significant results. In 9 trials with a total of 139 subjects, mean difference could be calculated; weighted for study size, it was 29% [range 24%–74%]. Willingness to drive was significantly greater in 4 of 6 studies including a total of 105 subjects; weighted mean difference increased by 207% [range 79–300%]. By contrast, measure of driving ability in three groups of a total of 200 trials in 57 subjects showed worse performance by a weighted mean of 96% [range 3–566%]. In three trials that tested inhibitory control (cued go or no-go response times), weighted mean performance was 30% [range 14-65%] worse on the descending limb. Conclusion: The 'Mellanby effect' has been demonstrated for subjective intoxication and willingness to drive, both of which are more affected at a stated ethanol concentration when BAC is rising than at the same concentration when BAC is falling. By contrast, objective measures of skills necessary for safe driving, such as response to inhibitory cues and skills measured on driving simulators, were generally worse on the descending part of the BAC-time curve for the same BAC.

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Abstract

Objective: To review the evidence for 'the Mellanby effect,' that is, that the response to a given blood alcohol concentration (BAC) is more marked when BAC is rising than at the same concentration when BAC is falling.

Methods: We systematically searched the databases EMBASE, Medline, and Scopus up to and including December 2016 using text words 'tolerance,' 'ascending,' 'descending' or 'Mellanby' with Medline term 'exp *alcohol/' or 'exp *drinking behavior/' or equivalent. Articles were identified for further examination by title or abstract; full text articles were retained for analysis if they dealt with acute (within dose) alcohol tolerance in human subjects and provided quantitative data on both the ascending and descending parts of the BAC–time curve. Reference lists of identified works were scanned for other potentially relevant material. We extracted and analyzed data on the subjective and objective assessment of alcohol effects.

Results: We identified and screened 386 unique articles, of which 127 full-text articles were assessed; one provided no qualitative results, 62 involved no human study, 25 did not consider acute tolerance within dose, and 13 failed to provide data on both ascending and descending BAC. We extracted data from the 26 remaining articles. The studies were highly heterogeneous. Most were small, examining a total of 770 subjects, of whom 564 received alcohol and were analyzed in groups of median size 10 (range 5–38). Subjects were often young white men, sometimes subdivided on the basis of drinking or family history. Doses of alcohol and rates of administration differed. Performance was assessed by at least 26 different methods, some of which measured many variables. We examined only results of studies which compared results for a given alcohol concentration (C) measured on the ascending limb (C_{up}) and the descending limb (C_{down}) of the BAC, whether in paired or parallel-group studies. When subjects were given alcohol in more than one session, we considered results from the first session only. Rating at C_{down} was better than at C_{up} for some measures, as expected if the Mellanby effect were operating. For example, subjects rated themselves less intoxicated on the descending limb than at the same concentration on the ascending limb in 12/13 trials including 229 subjects that gave statistically significant results. In 9 trials with a total of 139 subjects, mean difference could be calculated; weighted for study size, it was 29% [range 24%–74%]. Willingness to drive was significantly greater in 4 of 6

studies including a total of 105 subjects; weighted mean difference increased by 207% [range 79–300%]. By contrast, measure of driving ability in three groups of a total of 200 trials in 57 subjects showed worse performance by a weighted mean of 96% [range 3–566%]. In three trials that tested inhibitory control (cued go or no-go response times), weighted mean performance was 30% [range 14-65%] worse on the descending limb.

Conclusion: The 'Mellanby effect' has been demonstrated for subjective intoxication and willingness to drive, both of which are more affected at a stated ethanol concentration when BAC is rising than at the same concentration when BAC is falling. By contrast, objective measures of skills necessary for safe driving, such as response to inhibitory cues and skills measured on driving simulators, were generally worse on the descending part of the BAC-time curve for the same BAC.

Introduction

Ethanol (ethyl alcohol, 'alcohol') impairs cerebral function in a dose-dependent manner, at least at concentrations above a threshold of 50 mg/dL (0.050 g/dL) (1) (2). However, the relationship between blood alcohol concentration and cerebral function can be affected by prior alcohol exposure, as suggested by the apparent tolerance of chronic drinkers to very high concentrations (3).

The 'Mellanby effect' (4) or 'Mellanby phenomenon' (5) is the 'The purported phenomenon that the magnitude of behavioural impairment associated with a given blood alcohol concentration (BAC) is greater during a rising BAC than during a falling BAC.' The behavioural impairment may be objective (observed by others) or subjective (experienced by the drinker). In this context, the term 'acute tolerance' refers specifically to tolerance occurring within one session. (5)

Dr. (afterwards Sir) Edward Mellanby himself conducted a series of studies of alcohol absorption and elimination during the First World War. (6) Mellanby studied four fasted dogs ('Brown, Large Black, Small Black, White'), and administered various amounts (20–55 mL, equivalent to 1.5-–3.3 g/kg) of alcohol via oro-esophageal tube over several trials. He drew blood for BAC determination at 0.5, 1, 1.5, 2.5 hours, and then at 2–hour intervals after alcohol administration thereafter. He determined BAC by the potassium dichromate reduction method. He reported that alcohol peaked quite rapidly after consumption; that the BAC was proportional to the amount consumed; that consumption with milk inhibited intoxication by delaying GI absorption; and that dogs metabolize alcohol slowly, at a rate independent of the BAC (zero order kinetics). Mellanby noted the peak BAC ranged from 153- 530 mm^3/100 g blood (128 mg/dL to 445 mg/dL), and found a metabolic rate (15.7 mg/dL/hour) very similar

to the average rate in humans. He also disproved a belief common at the time that gulping all alcohol at once would produce less intoxication than would sipping the same amount over a longer period. Mellanby noted the difficulty assessing intoxication in dogs, because he was only able to use gross motor abnormalities as evidence of acute intoxication. These consisted of observations of scraping of the toe-nails on the floor while walking in the early stages of intoxication, hind leg weakness (most evident while standing still), and a 'rolling gait'; progressing to stumbling, difficulty getting up again after falling, and peaking with complete inability to walk and collapsing. These observed signs of intoxication disappeared about 2 hours after administration, and only lethargy and disinterest in the environment remained, with all other objective signs being normal. Using these observations, he was able to determine the BAC at which obvious intoxication occurred, and noted the intoxication was only observable on the ascending limb of the BAC–time curve. On the descending limb, when the same alcohol concentration was reached, the dogs appeared relatively normal. He postulated that the central nervous system was most affected initially by the 'sudden attack of the alcohol', or that the 'nervous system may re-learn to co-ordinate its activities after being under the alcoholic influence.' (6) (7)

Mellanby was well aware of the difficulties of determining the degree of intoxication in dogs, and of extrapolating his results to humans. In 1920 he presented the results of a further experiment, in which one (unidentified) man was asked to copy a drawing repeatedly after drinking '300 c.c. of [Imperial] proof spirit diluted to 900 c.c,' that is, approximately 170 mL pure ethanol (equivalent to approximately 10 standard drinks). (8) The changes in his ability to repeat the drawing varied with intoxication, but no conclusions could be drawn from an experiment with only one subject.

Here we consider the evidence that human subjects develop acute tolerance to the effects of alcohol, so that psychomotor impairment is greater at a given BAC when the concentration is rising ('the ascending limb of the alcohol curve') than at the same concentration when it is falling (the 'descending limb'). This postulated phenomenon of acute tolerance has been commonly referred to as the 'Mellanby Effect', but Sir Edward Mellanby, MD never referred to it as such.

Methods

We systematically searched the databases EMBASE, Medline, and Scopus from 1946 up to and including December 2016, using text words 'tolerance,' 'ascending,' 'descending' or 'Mellanby' with Medline term 'exp *alcohol/' or 'exp *drinking behavior/' or equivalent. We scanned reference lists of identified manuscripts meeting the criteria for other potentially relevant material. We identified articles for

further examination by the authors according to the title or abstract and retained full-text articles for further analysis if they dealt with acute (within dose) alcohol tolerance in human subjects, and provided quantifiable data on both the ascending and descending limbs of the BAC–time curve. In order to analyze data on the subjective and objective assessment of alcohol effects, we manually reviewed each eligible paper, extracted the data, and converted all recorded changes into percentage difference between ascending and descending limb. Due to the heterogeneity, meta-analysis could not be performed, but the data are presented in summary form as the attached table of the 26 eligible manuscripts. For the 'Mellanby Effect' of acute within-dose tolerance to be operating, the rating or measurement at C_{down} would have to be more nearly unimpaired (i.e., more sober) than at C_{up}.

Results

The database search identified an initial 386 unique articles. These were screened by title and abstract looking for objective measures in humans, and 127 full-text articles met this inclusion criterion and were read by the investigators. Of these 127, one provided no quantitative results, 62 involved no human study, 27 did not consider acute tolerance within dose, and 13 failed to provide data on both ascending and descending BAC. The remaining 26 articles were analyzed (9) (10) (11) (12) (13) (14) (15) (16) (17) (18) (19) (20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30) (31) (32) (33) (34). In addition, there were three articles containing information on trial subjects from two of these studies (35) (36) (37) .

The 26 studies we examined are listed in Table 3. The same subjects on both the ascending limb (C_{up}) and the descending limb (C_{down}) of the BAC-time curve were examined in 23, and there were 3 parallel-group studies (16) (19) (25) in which one group was examined on the ascending limb and another on the descending limb.

Researchers assessed the subjective state, cognitive function, and motor abilities by at least 26 different methods, some of which (e.g. simulated driving performance) measured many variables. These methods covered the five outcome domains described by Jongen (38). [Table 1]. The studies were highly heterogeneous, and most studies were small, with a median of only 10 subjects per group [range 5–56], and a total of 770 subjects. Study subjects were usually young white men, sometimes subdivided on the basis of drinking habits or family history, or both. Doses of alcohol and rates of administration differed. All effects seen were dependent on each subject's prior drinking history and the degree of intoxication.

Analyses sometimes considered changes from baseline, or compared tests with alcohol against placebo. This wide diversity among studies regarding ethanol dose, number of subjects, and experimental tests precluded us from performing a meta-analysis.

In most relevant studies, subjects rated themselves less intoxicated on the descending limb than at the same concentration on the ascending limb of the blood ethanol concentration–time curve, as expected if the Mellanby effect were operating. For example, considering those trials that gave statistically significant results: in 19 trials in 12 studies (9) (12) (13) (14) (17) (21) (22) (23) (24) (30) (33) (34) of a total of 229 subjects, the mean difference, weighted for study size, in the 9 trials providing numerical data, was 29% [range 24%–74%] less intoxicated subjectively. In four studies (9) (21) (30) (33), examining a total of 105 subjects, willingness to drive increased significantly in 4 of 6 trials. Weighted mean improvement in 52 subjects was 207% [range 79–300%]: that is, they were three times as willing to drive on the descending limb. By contrast, measure of driving ability in three groups of a total of 200 trials in 57 subjects (21) (30), showed worse performance by a weighted mean of 96% [range 3-566%]. In three trials (24) (25) (28) testing inhibitory control (cued go/no– go tests), weighted mean performance was 30% [range 14–65%] worse on the descending limb.

In some studies, minor objective measures showed improvement at C_{down} compared with C_{up}. The time for a maze task improved by a mean of 11% (13); and for a peg-board task improved by 71% (24). Arithmetic ability improved by 10% to 18% (18) abstraction by 21%, and attempts at abstraction by 182% (19). Results for several domains were inconsistent between studies.

Importantly, measure of driving ability such as lane deviation, line crossing, and speed deviations or excesses showed statistically significant deterioration on the descending limb. Three groups of a total of 200 trials on 57 subjects (21) (30), showed worse performance by a weighted mean of 96% [range 3–566%].

Discussion

Sir Edward Mellanby's observations on four dogs and one man, perhaps coupled with the subjective experiences of those investigators who had themselves drunk alcohol, have for nearly a century led to the view that the effects of a given BAC are dependent not only on the absolute value but also whether it is increasing or decreasing.

We have systematically reviewed the evidence for the Mellanby effect. We may have failed to find relevant studies, or have excluded them from analysis. However, we have considered both the references identified by our search and the reference lists of the papers relevant to our review. Firm conclusions are hampered by the relatively small number of studies, and the experimental difficulties. The optimal experimental design is uncertain, because repetition on the descending limb of a test already administered on the ascending limb inevitably introduces a possibility of short-term training effects. Prior training sessions and placebo studies help to mitigate this. Alternatively, parallel-group studies are possible. However, these are relatively insensitive, and therefore demand large groups for statistically robust results. The analysis of placebo-controlled studies is also complex; some authors have been meticulous in presenting detailed analyses of variance or co-variance, while failing to present tables of the measurements from which they are derived, so that absolute effect size cannot be estimated. In several studies, the measures of performance were only presented as graphs. Martin and Moss noted that the 'Mellanby measure' (of the effect at some concentration C on the descending limb minus the effect at the same concentration on the ascending limb) is potentially confounded by differences in the direction of change in BACs on the two limbs of the blood alcohol curve. (23) Early studies generally looked only at one concentration on the ascending limb and an approximately similar concentration on the descending limb. Designs using several data points could allow the slope of the BAC to be incorporated into the analysis. (23) An early study in a single subject presented results as hysteresis curves. (39) In a few modern studies, notably the study by Cromer et al, (13) plots showing multiple measures on both limbs demonstrate what are essentially clock-wise hysteresis curves.

The experimental studies may be difficult to generalize to real-world experience. Study subjects are demographically quite uniform—often young white men, and commonly college students. Some have personal or family histories of heavy drinking, which may be relevant factors in determining the responses. For example, results differed between groups considered 'at-risk' and 'non-risk' of alcohol-related disease (15). In addition, the pattern of drinking and the amount of alcohol consumed during studies probably differed substantially from real life conditions. In some studies, tests were repeated after an interval of some days, sometimes more than once, to examine 'sub-acute' tolerance. In those cases, we examined evidence only for the first study of such a series. Doses of ethanol differed substantially between studies, from 0.135 mg/kg (18) to 1.16 g/kg (32). Ethanol was administered

intravenously in one study (34). In addition, due to obvious safety concerns, most studies used a target peak BAC near 80 mg/dL, which is the limit above which driving is illegal in the United Kingdom and the USA. Mellanby observed dogs with BACs mainly in the range of 300– 450 mg/dL, much higher than examined in modern human experiments. It is unknown whether a 'Mellanby Effect' may be more easily demonstrable in humans when descending from these very high BACs. No experiments have tested this, and there are safety concerns for study subjects at these high BACs.

Some clear results have emerged from our review, in spite of the difficulties in interpreting the measurements from widely differing tests under many different conditions. The Mellanby effect was statistically significant and in favour of feeling more sober on the descending limb in 12 of 19 trials of the subjective feeling of intoxication, with only one result—after intravenous alcohol (34)—being statistically significant and in favour of subjectively feeling more drunk. The willingness to drive at a given BAC is twice as great on the descending limb as on the ascending limb, in parallel with the subjects feeling less drunk. The implication is that subjects almost always feel soberer on the descending limb, and therefore feel it is safer to drive. By contrast, the ability to drive, as judged by measures made during simulated driving, does not improve on the descending limb; it deteriorates substantially, with twice as many faults on the descending limb as on the ascending limb. The inevitable conclusion is that drivers who have taken alcoholic drinks contributing around 0.65–1 gram ethanol/kg bodyweight (which is 52– 80 g in an 80 kg person, roughly equivalent to 3½– 6 US standard drinks of 14 g each) and who are beginning to sober up are dangerous because their belief that they are less intoxicated is contradicted by a continued decline in driving skills.

The mechanism by which acute tolerance occurs is less clear. Neither breath nor blood alcohol concentrations reflect the instantaneous concentration at the site of action, presumed to be $GABA_A$ receptors in the central nervous system, and perhaps additional neuronal pathways (40). The disappearance of subjective effects could therefore be due to more rapid clearance of ethanol from the site of action than from the sampling site. However, this is unlikely to be the explanation, at least in rats (40). Kaplan et al gave a loading dose of oral ethanol to six male human subjects, followed by re-administration every 30 minutes to keep breath ethanol concentrations in the range of 80–100 mg/dL over the next six hours. They showed that even at steady state there is acute tolerance to the effects of alcohol on word recall; but no tolerance to measures of standing steadiness (body sway) or ability to maintain a simulated airplane on a centreline (41). Two more recent studies utilized an ethanol clamp in

which an IV ethanol load followed by a steady-state infusion produced nearly constant BACs for the study period, allowing the development of acute tolerance at constant BAC to be studied over time. Hendershot et al studied 88 young heavy drinkers (average age 19.8 years) who were given an intravenous load of ethanol sufficient to produce a BAC of 80 mg/dL in 20 minutes, followed by a steady-state infusion for 80 minutes to maintain the same BAC. They found response inhibition to a 'go/no go' test worsened as BAC rose, and continued to deteriorate during the steady-state phase (42). Zoethout et al studied 6 male and 6 female subjects aged 18–39 years. They gave a rapid infusion of ethanol over ten minutes, followed by a variable-rate infusion to maintain a BAC of 60 mg/dL for 5 hours. They found some parameters (visual analogue scale alertness, visual tracking, and body sway) fluctuated during the plateau phase, despite constant BrAC values. However, smooth pursuit eye movements remained impaired during the steady state (43). Interestingly, these constant BAC experiments failed to show acute tolerance to subjective feelings of intoxication, suggesting that changes in ethanol concentration, rather than absolute blood concentrations, determine subjective drunkenness. This makes sense logically, since as BACs rise, subjects feel increasing intoxication relative to when they started drinking, and as BACs fall, subjects notice a diminution of subjective intoxication as the time since peak BAC increases. For psychometric tests of performance, Schweizer and Vogel-Sprott argued that alcohol had a differential effect on reaction time, which is substantially improved on the descending limb compared with the ascending limb; and on accuracy, which is impaired to the same extent on both—what they term 'acute protracted errors.' (44). From this, they argue that alcohol may affect brain hemispheres differently, a hypothesis that has not yet been verified experimentally.

Conclusion

The so-called 'Mellanby effect' is most firmly established for subjective feelings of intoxication. Subjects feel less drunk and more able to drive during the descending limb of the BAC-time curve than at the same concentration of alcohol on the ascending limb. Since the effect is not seen when BAC is held constant, it may well be related to the rate and direction of change in BAC, rather than the development of acute tolerance to the drug effect.

Objective measures of impairment, especially those involving skills necessary for safe driving and those measured on driving simulators were generally worse during the descending limb for the same BAC. Slowed reaction times may recover somewhat during the descending limb, but accuracy falls. When these decrements are combined with a perceived improvement in ability to drive and a loss of inhibitory

control, the likelihood of driving while impaired increases, and may explain the binge or problem drinker's increased risks for motor vehicle crashes.

It appears then, that these objective tests are likely to be more robust than a person's own perception. The studies we have reviewed show that subjects feel less drunk during the descending limb of the BAC-time curve than at the same concentration of alcohol on the ascending limb. However, objective measures of impairment, especially those involving skills necessary for safe driving and those measured on driving simulators, were generally worse during the descending limb for the same BAC. All effects are dependent on a person's drinking history and the degree of intoxication.

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Table 1: Five major outcome domains

Derived from Jongen 2016 (38)

Outcome Domains	Tests used for assessment by included studies
A. Alertness/arousal	1. Pauli addition*
B. Attention & processing speed	2. Tracometer**
C. Reaction time/psychomotor function	3. Video game 4. Pursuit rotor test 5. Pegboard test 6. Proprioception 7. Vestibulo-ocular reflex 8. Skin conductance 9. Electromyogram
D. Sensory-perceptual functioning	10. Subjective intoxication 11. Willingness to drive
E. Executive functioning	12. Maze test 13. Cued Go/No-Go Test 14. Shipley IQ test 15. Memory scanning test 16. Random object scan test 17. Vocabulary test 18. Abstraction 19. Short-term memory 20. Information processing 21. Picture recognition 22. Word fragment 23. Free recall 24. Associative learning 25. Driving Simulation

*Pauli addition: study subjects find a solution to a problem by adding two numbers displayed in two different windows. **Tracometer: Study subjects track moving targets on a screen using a steering wheel

Table 2: Numbers of trials with results for effects on the ascending and descending limb demonstrating significantly 'improved' ('more sober'), non-significant, or significantly 'deteriorated' ('more drunk') results on the descending limb. (Not all studies in which results were statistically significant gave the numerical values for the results).

Test	Significantly improved ('more sober') during C_{down}	No difference	Significantly worse ('more drunk') during C_{down}
Subjective tests	16	8	1
Self-rated intoxication	12	6	1
Attention and processing		1	
Reaction time/psychomotor	7	7	
Executive function	9	26	16
Simulated driving		3	12

Table 3. Results from 26 trials examining the effect of alcohol both on the ascending and descending limbs of the blood alcohol concentration (BAC)–time curve, known as the 'Mellanby effect.'

Results are given as the mean percentage difference between measure on the ascending limb, taken as 100%, and the descending limb; statistical significance is quoted from the relevant studies.

A positive difference indicates that subjects felt more sober or that particular performance improved on the downward limb of the BAC–time curve.

	Number of subjects	Group sizes	Test(s)	Dose of ethanol	Mean percentage improvement Δ (descending limb – ascending limb)	Statistical Significance	Summary: Mellanby Effect
Amlung et al 2014	56 (26 F)	EtOH 28 Placebo 28	a. Perceived danger b. Willingness to drive Subjective intoxication	Calculated to produce a peak BrAC of 100 mg/dL	Δ = -50% Δ = + 300% Δ = -30%	P<0.001 P<0.001 P<0.01	Positive for subjective effects , but changes in the placebo group
Beirness et al. 1984	18 social drinkers	10 men 8 men	Tracometer	4 x 0.84 mL/kg	Mean Δ1% ± 4.93% Six worse, 12 better Graph shows % recovery to be -10% to +10%	NS	Not consistently demonstrated
Bennett et al. 1993	20	10 men 10 men	Video game	0.75 g/kg 1 g/kg	Mean Δ2–3%	NS	No
Benton et al. 1982	8	8 men	BrAC when sober Magnitude estimation (ME) of intoxication	2 x 0.65 mL/kg x 2 (2nd drink when BAC from 1st drink had	Day 1 Magnitude estimate after 1 drink (2nd drink given when ME was zero) mean Δ37% (felt better) Day 2 ME (2nd drink given when BrAC was zero)	P<0.03	Yes for subjective intoxication; second drink had less effect in both sessions
Cromer et al 2010	20	9 M, 11 F (all had ethanol then placebo, or the other way round)	Visual analogue scale (VAS) drunkenness; maze test Timed chase Time Total errors Exploratory errors	0 (placebo) 250 mL of vodka 40% and orange juice 60%	VAS Timed chase test Mean errors mean Δ7% Mean time mean Δ21% "There was no significant difference between limbs of the blood alcohol concentration (BAC) curve for total errors (A), exploratory errors (B), or exploratory errors on the delayed trial (C). Thus, measures of higher order cognition do not show an acute tolerance effect."	P<0.05 P=0.05 NS NS NS	Yes for subjective intoxication Yes for visuomotor speed and visuospatial learning No for higher cognitive function

6.	Fillmore et al. 2005	20	12 M 8F	Cued go-no go VAS 14-point Biphasic Alcohol Effects Scale	0.65 g/kg 0 g/kg	Reaction time Go mean Δ4.6% Reaction time No-go mean Δ0% Failure to inhibit Go mean Δ −32% Failure to inhibit No-go mean Δ0% Stimulation mean Δ39% Sedation mean Δ −19% VAS mean Δ24%	<0.01 NS NS NS P<0.01 NS NS	Yes (minor) for reaction time. No for inhibitory control Yes subjective stimulation by alcohol
7.	Fillmore et al. 2012	40	10 M 10F at risk 10M, 10F no risk	Pegboard task – Cued go/no go	0.65 g/kg 0 g/kg	At risk drinkers Pegboard Time mean Δ4% Reaction time mean Δ −1% (Anti-Mellanby) Non-risk Pegboard Time mean Δ0% Reaction time mean Δ0%	P=.002 P=0.03 NS NS	Yes (very minor) for pegboard test in binge drinkers No for reaction time No for non-risk drinkers
8.	Haubenreisser et al. 1983	25 (only 20 had ethanol)	10 M ascend 10 M descend 5 M placebo	Pursuit rotor test	0.83 mL/kg	First session: mean Δ0%	NS	No
9.	Hiltunen et al. 1997	10	5 moderate 5 light	Pauli addition Pursuit Rotor Pauli addition Pursuit Rotor	0.5 – 1.0 g/kg	Pauli addition 0.5g ethanol/kg Light consumers mean Δ10% Moderate consumers mean Δ0% 1g ethanol/kg Light consumers mean Δ18% Moderate consumers mean Δ16% Pursuit rotor 0.5g ethanol/kg Light consumers Duration mean Δ70% Frequency mean Δ64% Moderate consumers, Duration mean Δ58 Frequency mean Δ −49% Pursuit rotor 1g ethanol/kg Light consumers Duration mean Δ41%	 P=0.02 NS P=0.01 NS P=0.03 NS NS NS P=0.02 P=0.049	Yes for simple math problems, only at low dose alcohol No- more misses for pursuit rotor skills at low dose alcohol Yes at higher dose alcohol

						Frequency mean Δ28% Moderate consumers Duration mean Δ31% Frequency mean Δ28%	NS P=0.03	
10.	Hiltunen 1997	10	5 mod 5 light	VAS degree of intoxication (presented graphically)	0.5 – 1.0 g/kg	0.5g ethanol/kg Light consumers VAS Δ40% Moderate consumers VAS Δ16% 1g ethanol /kg Light consumers VAS mean Δ60% Mod consumers VAS mean Δ74%	0.02 NS P<0.05 P<0.05	Yes- subjective for light drinkers at low dose and moderate drinkers at all doses No- subjective for high dose in light drinkers
11.	Jones et al. 1972	40 (only 20 had ethanol)	10 10 10 10	Shipley Errors	1.254 mL/kg	Vocab Abstraction mean Δ21% Errors of commission Errors of omission mean Δ79% Raven's progressive matrices mean Δ0%	NS P<0.05 NS P<0.01 NS	Yes- for abstraction and errors of commission
12.	Jones 1973	40 (only 20 had ethanol)	20 20	Verb mem-immediate verbal mem – short verbal mem - med	0 1.254 mL/kg	Immediate memory mean Δ9% Short term mean Δ11% Long term mean Δ32%	<0.01 NS NS	Yes for immediate memory only
13.	Marczinski Et al. 2009	28	18 binge 10 non-binge	Intox scale Willingness to drive Simulated driving	0 0.65 g/kg	Binge drinkers Intox mean Δ38% Willingness to drive mean Δ85% Non-binge drinkers Intox mean Δ22% Willingness to drive mean Δ −22% (anti-Mellanby) Binge drinkers Lane deviation mean Δ −11% (anti-Mellanby) Centre line crossing mean Δ -64% (anti-Mellanby) Road edge excursions mean Δ -95% (anti-Mellanby) Driving speed deviation mean Δ4% Non-binge Lane deviation mean Δ -43% (anti-Mellanby) Centre line crossing mean Δ -310% (anti-Mellanby) Road edge excursions mean Δ -47% (anti-	P<0.001 unstated NS unstated See below See below	Yes for feelings of intoxication and willingness to drive in binge drinkers only, not in non-bingers

						Mellanby) Driving speed deviation mean Δ -45% (anti-Mellanby) Both mean Δ -22% (anti-Mellanby) mean Δ -3% (anti-Mellanby) mean Δ -110% (anti-Mellanby) mean Δ -75% (anti-Mellanby)	Both P<0.001 P=0.004 P=0.004 NS	No for driving impairment, worse on descending limb
14.	Martin & Earleywine 1990	58	10M beer 10M vodka 38M vodka	Music rating Intox scale Accuracy of BAC Intox scale	0.85 mL/kg slow 0.75 mL/kg fast	Time to peak BrAC > time to peak drunkenness 60.0 (9.7) -v- 64.5 (8.6) minutes Return to baseline 148 (36.1) -v- 89.9 (29.5) Δ39% (better) Time to zero BrAC > time to zero drunkenness 51.2 (21.1) -v- 31.2 (30.6) Δ20% 204.9 (100.8) -v- 102.3 (79.8) Δ50%	NS <0.001 <0.001 <0.001	Yes but only for subjective feeling of intoxication
15.	Martin & Moss 1993	20	20 M	Subjective intoxication, using the 100-mm analog	0 0.135 mg/kg 0.27 g/kg 0.8 g/kg	–. – – 12/15 better on ↓ 17/20 scores above 1.0 "Present results suggest a relation between rate of alcohol consumption, the slope of rising BACs, and the time of peak intoxication."	– – – NS P<0.05	No effect for most measures
16.	Ostling & Fillmore 2010	32 (only 16 had ethanol)	16M 16F	Cued go/no go Grooved pegboard Intox scale Subjective intox	0.65 g/kg	Reaction time mean Δ16% Inhibitory failure mean Δ −29% (Anti-Mellanby) Pegboard performance mean Δ71% Felt less impaired mean Δ27%	P<0.03 ?NS P<0.01 P<0.01	Yes for subjective impairment and reaction time No for inhibition
17.	Pihl et al. 2003	41 (only 21 had ethanol)	11 ascend 10 descend	Six games [Four variations of the Random Object Span Task (ROST) and two variations of the	1.254 mL/kg	Trials to complete mean Δ −60% (anti-Mellanby) "Both alcohol dose groups were **significantly**	<0.01 Med	No for executive cognitive functioning

				Acquired Association Task were presented sequentially to the participants.]		**slower** on the Timed Chase Test during descending BACs compared with their performance on the ascending limb.“ “In addition, the Medium group made **significantly more errors** on the Timed Chase Test on the descending limb”	P=0.05 High P=0.008 P=0.021	
18.	Pishkin et al. 1983	40 (of whom 20 had ethanol)	10 (success feedback) 10 (failure feedback)	EMG Skin conductance Vocab Abstraction	1.32 ml of 95% USP ethanol per kg of body weight	Skin conductance mean Δ25% Non-statistically-significant trend in all other parameters	<0.01	Yes for skin conductance-none for behaviour
19.	Post et al. 1998	8	6F 2M	Apparent concomitant motion as measured by Vestibulo ocular reflex		VOR better on descending limb when there was feedback but not when it was absent Apparent concomitant motion towards baseline quicker than BAC. mean Δ Slope 0.16%/min	<0.01 P<0.5	Yes, but only with feedback
20.	Schweizer et al. 2006	20 (of whom 10 had ethanol)	10M	Short term memory Information process (18 tests altogether)	0.65 g/kg	Short term memory Visual-spatial working memory Inhibitory control: Mean response times hardly changed and % errors increased on descending	NS NS	No; and percent errors increased
21.	Soderlund et al. 2005	64 (of whom 32 had alcohol)	32M ethanol 32M placebo	Picture recognition Word fragment Free recall Associative learning	1mL/kg Or Placebo	Picture recognition: no effect Word fragment completion Free recall ↓ better than ↑ for encoding, alcohol group having fewer hits than the placebo group on the ascending but not the descending limb.	NS NS NS P<0.05	Yes for encoding and word recognition
22.	Starkey & Charlton 2014	61 [29 in ethanol analyses]	33M 28F 14 mod 15 high (12 participants not analyzed) 20 placebo	Simulated drive (DAIR) Cognitive tests Subjective rating	0.6 g/kg or 0.75 g/kg women 0.75 g/kg or 1.0 g/kg men (to achieve medium BAC 0.05g%, or high BAC 0.08g%)	Maximum speed while driving, number of edge line crossings, time over the edge line, the SD of lane position, number of responses to false alarm vehicles, the number of rule break errors number of maze recall errors Worse ↑ than ↓ subjective intoxication willingness to drive	NS P<0.05	Yes for subjective impairment;

						Worse ↓ than ↑ chase moves chase task errors Maze total errors Speed over 100 km/h Centre line crossing Seconds over centre line Medium (50mg/dL) Acute tolerance Subjective intoxication mean Δ26% Willingness to drive mean Δ79% "Acute protracted error" Chase task errors mean Δ −566% Sec over 100kmh mean Δ −44% High (ethanol 80 mg/L) Acute tolerance Subjective intox mean Δ0% Willingness to drive mean Δ2% Acute protracted error Chase moves mean Δ8% Chase task errors mean Δ −176% GMLT total errors mean Δ −18% Sec over 100kmh mean Δ −21% Sec over centreline mean Δ −15%	P<0.05 All P<0.05 NS NS All P<0.05	No: many aspects of driving and cognitive performance worsened on descending limb
23.	Vogel-Sprott 1979	10 (of whom 5 had ethanol)	5M	4 sessions: Pursuit rotor task Coding task	0.88 94.6% ethanol (A) mL/kg Or placebo (P)	Early sessions ethanol worse than placebo both ascending and descending Pursuit rotor: No evidence for acute tolerance coding mean Δ142% alcohol worse than placebo descending alcohol = placebo descending	P<0.01 NS P<0.05	No for the psychomotor task (rotor) Yes for cognitive (coding)

24.	Wang et al 1993	7	7M	Proprioception measured at BAC of 0.05g% and 0.075g%	1.23 g/kg	Errors 50 mg/dL mean Δ27% 75 mg/dL mean Δ23% 50 mg/dL -v- 75mg/dL	P<0.001 P<0.007 P<0.001	Yes for proprioceptive response
25.	Weafer & Fillmore 2012	20	10M 10F	Computer drive Cued go/no-go Willingness VAS Inhibitory Pegboard Intox VAS	0.65 g/kg or 0	LPSD 1.29→1.22 Line cross 3.95→3.60 Steer rate 3.95→3.60 **Increased p-fails mean Δ −14%** Reaction time mean Δ0% Willingness 17.1→38.9 mean Δ127%	NS NS NS P<0.05 NS P<0.01	Yes for subjective impairment; no for driving performance & inhibitory control
26.	Wetherill et al. 2012	54	27 family history positive 27 family history negative	Feeling intox Feeling high Feeling sedated Feeling stimulated		Moderate drinkers felt more intoxicated on the ascending slope, while light drinkers felt more intoxicated on the descending slope. (Figure 2A) Mean perceptions Family history positive Intox mean Δ −18% High mean Δ −3% Stimulation mean Δ −2% Sedation mean Δ4% Family history negative Intox mean Δ0% High mean Δ −6% Stimulation mean Δ4% Sedation mean Δ14% Light drinkers Intox mean Δ −25% High mean Δ −33% Stimulation mean Δ −23% Sedation mean Δ −12% Moderate drinkers Intox mean Δ5% High mean Δ14%	P<0.023 P<0.023	Yes for moderate drinkers, who were subjectively less impaired on descending; no for light drinkers, who were more impaired

						Stimulation mean Δ15% Sedation mean Δ27%		

Figure 1: Review Strategy- Mellanby —Acute Alcohol Tolerance — Articles Identified