CHAPTER 9

Pharmacokinetics and central nervous system effects of the novel dopamine D3 receptor antagonist GSK598809 and intravenous alcohol infusion at pseudo-steady state

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ABSTRACT

GSK598809 is a novel selective dopamine D_3 receptor antagonist, currently in development for treatment of substance abuse and addiction. In a blinded, randomized, placebo-controlled study, effects of single oral doses of 175 mg GSK598809 were evaluated in healthy volunteers. Pharmacokinetics, central nervous system (CNS) effects and potential for interactions with alcohol were evaluated, using an alcohol infusion paradigm and analysis of eye movements, adaptive tracking, visual analogue scales, body sway, serum prolactin and verbal visual learning test. Adverse effects of GSK598809 included headache, dizziness and somnolence. Plasma concentration of GSK598809 was maximal 2-3 hours postdose and decreased with a half life of roughly 20 hours. CNS effects were limited to prolactin elevation and decreased adaptive tracking. Co-administration of GSK598809 and alcohol did not affect alcohol pharmacokinetics, but caused a 9% decrease of C_{max} and a 15% increase of AUC of GSK598809. CNS effects of co-administration were mainly additive, except a small supra-additive increase in saccadic reaction time and decrease in delayed word recall. In conclusion, GSK598809 causes elevation of serum prolactin and a small decrease in adaptive tracking performance. After co-administration with alcohol, effects of GSK598809 are mainly additive and the combination is well tolerated in healthy volunteers.

INTRODUCTION

A large body of evidence indicates that the mesolimbic dopaminergic pathway, which includes dopaminergic neurons in the ventral tegmental area projecting to the nucleus accumbens and other limbic forebrain structures, is one of the major neuronal circuits involved in the acute rewarding effects of drugs of abuse (Cami and Farre, 2003; Hyman and Malenka, 2001; Hyman, 2005; Koob and Nestler, 1997; Koob *et al.*, 1998). Although addictive drugs interact with many different neurotransmitter systems, most drugs ultimately cause an acute increase in synaptic dopamine in the nucleus accumbens and the mesolimbic dopaminergic system (Koob and Bloom, 1988; Nestler, 2005; Pierce and Kumaresan, 2006), as demonstrated by microdialysis studies in rats (Di Chiara and Imperato, 1988) and positron emission tomography (PET) studies in humans (Volkow *et al.*, 1999; Volkow *et al.*, 2003; Volkow *et al.*, 2004; Volkow *et al.*, 2007; Volkow *et al.*, 2009). Several important observations have suggested that dopamine D_3 receptors may play a significant role in the effects of drugs of abuse and the pathophysiology of drug addiction (Heidbreder *et al.*, 2005; Le Foll *et al.*, 2005). First, dopamine D_3 receptors are located primarily in mesolimbic regions such as nucleus accumbens and ventral striatum (Gurevich and Joyce, 1999; Herroelen *et al.*, 1994; Landwehrmeyer *et al.*, 1993; Murray *et al.*, 1994; Seeman *et al.*, 2006). Second, studies in animal models have demonstrated that dopamine D_3 receptor activation may be involved in the reinforcing effects and self-administration of cocaine (Caine and Koob, 1993). Third, long term drug exposure appears to cause upregulation of dopamine D_3 receptors as demonstrated in postmortem studies of cocaine overdose fatalities (Segal *et al.*, 1997; Staley and Mash, 1996). Accordingly, it has been suggested that dopamine D_3 antagonism may be an effective strategy in pharmacotherapy of addiction (Heidbreder *et al.*, 2005; Joyce and Millan, 2005; Levant, 1997).

GSK598809 is a novel, potent and selective dopamine D_3 receptor antagonist (Searle *et al.*, 2010), which is being developed as a novel treatment for substance dependence disorders. Functional assays showed that GSK598809 has greater than 100-fold selectivity for dopamine D_3 receptors over dopamine D_2, histamine H_1, muscarinic M_1, M_2, M_3, M_4, serotonin 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors (data on file). Conditioned place preference (CPP) experiments in animal models indicated that GSK598809 significantly reduced nicotine- and cocaine-seeking behavior in a dose-dependent manner (data on file). In addition, GSK598809 significantly prevented relapse to nicotine-seeking behavior, although no effect was observed on reducing alcohol consumption in rats (data on file).

The present study was performed to evaluate the pharmacokinetics and central nervous system (CNS) effects of single oral doses of GSK598809 in

healthy volunteers. Special emphasis was given to evaluating possible interactions with alcohol, because the target population of patients will have alcohol dependence as primary disorder, or may abuse alcohol as comorbidity next to another substance abuse disorder. Pharmacokinetic interactions between alcohol and GSK598809 are theoretically possible, because a metabolite of GSK598809 shows *in vitro* to have a potential for inhibiting CYP2E1, which is one of the main enzymes involved in alcohol metabolism (Lieber, 1997). Also, pharmacodynamic interactions are theoretically possible as both compounds are centrally active and influence the dopamine system. However, apart from these theoretical possibilities, there are no reasons to assume *a priori* that any specific pharmacodynamic interaction will occur between GSK598809 and alcohol. Currently, no validated human pharmacodynamic markers for dopamine D_3 antagonism are available. For exploratory purposes, we used a battery of quantitative central nervous system tests, sensitive to various compounds, including alcohol (Zoethout *et al.*, 2009) and antipsychotic drugs (dopamine D_2 receptor antagonists) (de Visser *et al.*, 2001), was used to evaluate pharmacodynamic effects. An oral dose of 175 mg GSK598809 was chosen because positron emission tomography using [^{11}C]-(+)-PHNO in healthy volunteers has demonstrated that this dose can induce high occupancy (near 100%) of dopamine D_3 receptors in the substantia nigra (Searle *et al.*, 2010). Also, previous studies in healthy volunteers demonstrated that this dose is generally well tolerated (data on file).

METHODS

Study design

Twenty healthy volunteers, between 18 and 65 years of age and with a body mass index (BMI) between 18 and 30 kg/m^2, were planned to participate in a blinded, randomized, placebo-controlled, double-dummy, four-period crossover study. The study was approved by the medical ethics review board of the Leiden University Medical Center and registered at the NIH database of clinical trials (website http://clinicaltrials.gov) with identifier NCT00887367 and GSK ID number 106591. Prior to medical screening, all volunteers gave written informed consent. All volunteers underwent training sessions for the pharmacodynamic tests in order to minimize possible learning effects.

Volunteers were assigned to a randomized treatment sequence (see figure 1), consisting of one period of oral administration of 175 mg of GSK598809 combined with intravenous alcohol infusion (alcohol clamping, see below for further details), one period of oral administration of 175 mg of GSK598809 combined with intravenous placebo infusion, one period of oral placebo administration combined with intravenous alcohol infusion, and one period with oral placebo administration combined with intravenous placebo infusion. This study design enables analysis of the following comparisons (see figure 1):

1 Administration of 175 mg GSK598809 (n = 20) versus placebo (n = 20) Intravenous alcohol infusion (n = 20) versus placebo (n = 20)
2 Co-administration of 175 mg GSK598809 and intravenous alcohol infusion (n = 20) versus placebo (n = 20)
3 Co-administration of 175 mg GSK598809 and intravenous alcohol infusion (n = 20) versus intravenous alcohol infusion alone (n = 20)

GSK598809 or matching placebo was administered orally 30 minutes after the start of the ethanol (or placebo) infusion. The alcohol (or placebo) infusion continued for 5 hours in total to cover the main part of the plasma concentration curve of GSK598809. Each study period consisted of five study days. The randomized treatment was administered in the morning of the first study day, followed by pharmacokinetic and pharmacodynamic measurements at regular time points. All periods were separated by a washout time of at least five days.

Occasional (non-daily) smokers were eligible to participate in the study. Subjects were excluded from participation if they smoked on a daily basis. Also, subjects were excluded if they had an average daily intake of greater than 2 units (in case of females) or 3 units (in case of males) or an average weekly

alcohol intake of greater than 14 units (in case of females) or 21 units (in case of males). One unit is equivalent to a half-pint (220 mL) of beer or 1 (25 mL) measure of spirits or 1 glass (125 mL) of wine. Subjects were instructed to abstain from smoking and alcoholic drinks on the day preceding all study periods and all subsequent study days. In addition, use of illicit drugs was not permitted. In all study periods, breath alcohol measurements were performed to ascertain non-use of alcohol. Also, urine drug screening for cocaine, amphetamines, opiates (morphine), benzodiazepines, barbiturates and THC (Innovacon, Inc., San Diego, California, USA) was performed to ascertain non-use of illicit drugs.

Alcohol clamping

The method for attaining constant alcohol levels has been described in detail elsewhere (Zoethout *et al.*, 2008; Zoethout *et al.*, 2009). In brief, alcohol (ethanol 10% w/v solution in 5% glucose) was infused intravenously over a period of five hours, guided by breath alcohol measurements to maintain a pseudo-steady state alcohol serum level of 0.6 g/L. This target level was chosen because this level produces significant central nervous system effects without causing too many inadvertent effects and is considered safe, since it is only just above the legal driving limit in the Netherlands (i.e. 0.5 g/L). Alcohol infusion started 30 minutes prior to administration of GSK598809. The infusion rate for the first ten minutes was determined using demographic data of the volunteer (weight, height, age and gender). Infusion rates were subsequently adjusted, guided by breath alcohol measurements at baseline and at every five minutes for the first 30 minutes after the start of the infusion, every 10 minutes for the next 30 minutes and then every half hour until the end, using two calibrated Alco-Sensor IV Intoximeters (Honac, Apeldoorn, the Netherlands), which were alternated to avoid fatigue of the sensors. To prevent local pain at the beginning of the alcohol infusion, an additional diluting glucose 5% infusion at 100 mL/h was given to all participants during the first 10 minutes after the start of the alcohol infusion over the same infusion line. Alcohol clamping was performed in a randomized, double-blind, placebo-controlled fashion by an infusion assistant, who was not a member of the study team. A sham procedure, consisting of saline infusion in a manner similar to the alcohol infusion, including repeated breath alcohol measurements and subsequent infusion rate adjustments, was used to maintain blinding of the subject and the rest of the team. The mock infusion rate adjustments were provided by the clamping program.

Safety monitoring

Evaluation of adverse events, 12-lead electrocardiograms (ECG), blood pressure, heart rate, alcohol breath test, urinalysis and blood sampling for haematology and chemistry was performed at regular time points after each dose administration. Automated oscillometric blood pressures were measured using a Nihon-Kohden BSM-1101K monitor or a Colin Pressmate BP 8800. ECGs were obtained with Cardiofax V equipped with ECAPS12 analysis program (Nihon-Kohden, Tokyo, Japan). In addition, telemetry monitoring was started at the beginning of alcohol infusion and was continued for six hours. Volunteers were evaluated for akathisia and extrapyramidal symptoms, using the Barnes Akathisia Rating Scale (Barnes, 1989), Simpson-Angus Scale (Simpson and Angus, 1970) and Abnormal Involuntary Movement Scale (Munetz and Benjamin, 1988).

Pharmacokinetics

Venous blood samples for GSK598809 concentration analysis were collected prior to dose administration and at 15 and 30 minutes and 1, 2, 3, 4, 6, 8, 10, 12, 24, 48 and 72 hours after dose administration. Concentration of GSK598809 in plasma samples was determined using protein precipitation followed by HPLC/MS analysis with a lower limit of quantification (LLQ) of 0.5 ng/mL. Pharmacokinetic parameters of GSK598809 include the maximum observed plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), area under the plasma concentration-time curve extrapolated to infinity (AUC_{∞}) and terminal phase half life ($t_{½}$).

Venous blood samples for pharmacokinetic analysis of serum alcohol were taken prior to start of infusion and at 15, 30, 45, 60, 90, 150, 210, 270 and 390 minutes after start of alcohol infusion. Serum alcohol levels were measured with an enzymatic assay (Roche Diagnostics, Mannheim, Germany) using a Hitachi 911 (Boehringer Mannheim, Mannheim, Germany). In this enzymatic assay, alcohol and nicotinamide adenine dinucleotide (NAD^+) are converted to acetaldehyde and NADH by alcohol dehydrogenase (ADH). The NADH formed during the reaction, measured photometrically as a rate of change in absorbance, is directly proportional to the alcohol concentration.

Pharmacodynamic testing

All pharmacodynamic measurements were performed as described previously (de Haas *et al.*, 2009; Liem-Moolenaar *et al.*, 2010a). Volunteers were tested individually in a quiet room with ambient illumination. Quantitative tests, sensitive to the effects of alcohol (Zoethout *et al.*, 2009) and single oral doses of antipsychotic drugs (dopamine D_2 receptor antagonists) (de Visser *et al.*, 2001) such as haloperidol (Liem-Moolenaar *et al.*, 2010a; Liem-Moolenaar *et al.*, 2010b) and risperidone (Liem-Moolenaar *et al.*, 2011) in healthy volunteers, included measurements of smooth pursuit and saccadic eye movements, adaptive tracking, body sway, visual analogue scales, the visual verbal learning test (VVLT) and serum prolactin levels. Previous studies using the alcohol clamping paradigm and this pharmacodynamic test battery (Zoethout *et al.*, 2009) demonstrated that smooth pursuit eye movements and body sway were the most sensitive pharmacodynamic parameters for the effects of alcohol. In order to obtain accurate time profiles of the effects of alcohol and GSK598809, smooth pursuit eye movements and body sway were recorded at a high frequency. The other pharmacodynamic tests could not be performed as frequently due to limitations in time and logistics.

ANALYSIS OF EYE MOVEMENTS To evaluate oculomotor performance and sedation, smooth pursuit and saccadic eye movements were recorded as described previously (Baloh *et al.*, 1975; Bittencourt *et al.*, 1983; van Steveninck *et al.*, 1991; van Steveninck *et al.*, 1999), using a microcomputer-based system for data recording and analysis (Cambridge Electronic Design Ltd., Cambridge, UK), Nihon-Kohden equipment for stimulus display, signal collection and amplification (Nihon-Kohden, Tokyo, Japan), and disposable surface electrodes (Medicotest N-00-S, Olstykke, Denmark). For smooth pursuit eye movements, a target light source moves sinusoidally over 20° eyeball rotation at frequencies ranging from 0.3 to 1.1 Hz. The time in which the eyes were in smooth pursuit was calculated for each frequency and expressed as the percentage of stimulus duration. The average percentage of smooth pursuit for all frequencies was used as parameter. Smooth pursuit eye movements were recorded prior to dose administration and at 10, 20, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420 and 450 minutes after dose administration. For saccadic eye movements, the target light source jumps from side to side. Peak velocity (degrees per second), reaction time and inaccuracy (%) was calculated of all artifact-free saccades. Saccadic eye movements were recorded prior to dose administration and at 30, 90, 150, 210, 270, 330, 390 and 450 minutes after dose administration.

ADAPTIVE TRACKING To evaluate visuo-motor coordination, the adaptive tracking task was performed as described previously (Borland and Nicholson, 1984; Gijsman *et al.*, 1998; van Steveninck *et al.*, 1991; van Steveninck *et al.*, 1993; van Steveninck *et al.*, 1999), using customized equipment and software developed by K.W. Hobbs (Hertfordshire, UK). Adaptive tracking is a pursuit tracking task in which a circle moves randomly over a computer screen and the volunteer must try to keep a dot inside the moving circle using a joystick. If this effort is successful, the speed of the moving circle is increased and if the effort is unsuccessful, the speed is reduced. The adaptive tracking task was performed prior to dose administration and at 30, 90, 150, 210, 270, 330, 390 and 450 minutes after dose administration and performance was scored over a fixed period of three minutes. Average performance and standard deviation of scores were used for analysis.

BODY SWAY Postural stability in the sagittal plane was measured with an apparatus similar to the Wright ataxiameter (Wright, 1971), using a string attached to the waist of the volunteer. Measurements were performed prior to dose administration and at 10, 20, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420 and 450 minutes after dose administration. Movements over a period of two minutes, while standing still with eyes closed, were integrated and expressed as mm sway.

VISUAL ANALOGUE SCALES Subjective effects were quantified prior to dose administration and at 30, 90, 150, 210, 270, 330, 390 and 450 minutes after dose administration using a Dutch translation of the visual analogue scales (VAS), originally described by Norris (Norris, 1971), to derive three composite factors corresponding to alertness, mood (contentedness) and calmness, as described by Bond & Lader (Bond and Lader, 1974). In addition, a visual analogue scale was used to quantify the subjective effects of alcohol.

VISUAL VERBAL LEARNING TEST The visual verbal learning test (VVLT) (Schmitt *et al.*, 2000) is an adapted version of the auditory verbal learning test (Rey, 1964) and was performed 150 minutes after dose administration. Three trials of 30 words are presented on a computer screen in the same sequence. The volunteer is requested to reproduce as many words as possible at the ending of each trial (immediate recall) and after 30 minutes (delayed recall). The number of correctly reproduced words is analyzed for each trial. Also, a recognition test is performed, consisting of 15 previously presented words and 15 new words, in which the volunteer has to indicate recognition of the word (delayed recognition) as quickly as possible. Response time and the number of correctly recognized words are analyzed.

SERUM PROLACTIN LEVELS Blood samples for measurement of prolactin levels were collected at baseline and at 60, 90, 120, 210, 390, 720 and 1320 minutes after study drug administration and serum was separated by centrifugation (2000 g at 4°C for 10 minutes). Prolactin levels were determined using an electrochemiluminescence immunoassay (ECLIA) on a Modular Analytics E170 (Elecsys module) immunoassay analyzer.

Statistical analysis

Analysis of variance models were performed on the pharmacokinetic parameters, including the factors treatment and period as fixed effects and subject as random effect. AUC and C_{max} pharmacokinetic parameters were log-transformed prior to analysis. Comparisons were expressed as ratios of the pharmacokinetic parameters after GSK598809 combined with ethanol relative to those after alcohol alone or relative to those after GSK598809 alone.

Pharmacodynamic data were compared using a mixed model analysis of variance with treatment, gender, period, time, and treatment by time as fixed factors, and with subject, subject by treatment and subject by time as random factors. VVLT data were compared using a mixed model analysis of variance with treatment, gender and period as fixed factors, and with subject as random factor. The parameters body sway, prolactin, saccadic eye movements and the delayed word variables were log-transformed prior to analysis to correct for the expected log-normal distribution of the data. The following contrasts were calculated (see figure 1): alcohol versus placebo, GSK598809 versus placebo, co-administration of GSK598809 and alcohol versus placebo, co-administration of GSK598809 and alcohol versus alcohol alone.

Supra-additive effects (defined as effects, resulting from co-administration of two independent agents, being greater than the sum of effects of each individual agent) were evaluated by analyzing the contrast of the effects of co-administration of GSK598809 and alcohol with subtraction of the effects of GSK598809 alone versus the effects of alcohol alone with subtraction of the effects of placebo.

After identifying gender effects on prolactin levels, analysis of prolactin data was repeated using a mixed model analysis of variance with treatment, gender, period, time, treatment by gender, treatment by time, gender by time and treatment by gender by time as fixed factors, and with subject, subject by

treatment and subject by time as random factors. Contrasts were calculated in original measurement unit with 95% confidence intervals and the associated *p*-value, except for the log-transformed parameters, which were calculated as a percentage relative to placebo or alcohol. All calculations were performed using SAS for Windows version 9.1.3 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Subjects

Twenty volunteers (10 males and 10 females) were included in the study. Volunteers had a mean age of 32.8 years (range 18-55), weight of 73.5 kg (range 54-108) and body mass index (BMI) of 23.6 kg/m² (range 18.5 - 29.8). One female volunteer tested positive for benzodiazepines on the drug screen in study period 2 and thereby violated the exclusion criteria. She was subsequently withdrawn from the study and not replaced. This volunteer was administered alcohol infusion and placebo capsules in the first study period.

Clinical observations

All adverse events were transient and mild or moderate in severity and no serious adverse events occurred during the study. Overall, the most frequent adverse effect were headache, somnolence, feeling drunk, dizziness, fatigue, pain at infusion site, nausea and vomiting (see table 1). Somnolence and fatigue were reported more frequently after GSK598809 administration combined with alcohol (n = 18), compared to alcohol alone (n = 8), GSK598809 alone (n = 4) or placebo (n = 4). There were no consistent and clinically relevant changes on the Barnes Akathisia Rating Scale, Simpson-Angus Scale and Abnormal Involuntary Movement Scale. Mild short-lasting akathisia was reported spontaneously once after administration of GSK598809 combined with alcohol and once after GSK598809 alone, but these events were not verified objectively by the Barnes Akathisia Rating Scale, when this was performed as scheduled. There were no consistent and clinically relevant changes in vital signs, blood chemistry and haematology or any of the ECG intervals.

Pharmacokinetics of alcohol

Following intravenous infusion, serum alcohol concentration increased rapidly and remained constant at the target level all over the time of infusion, after which serum concentrations declined (see figure 2).

Pharmacokinetics of GSK598809

Pharmacokinetic parameters are presented in table 2. Oral administration of GSK598809 resulted in peak levels after roughly 2 to 3 hours (see figure 3) with an apparent bi-exponential decline and a half life of roughly 20 hours.

Pharmacokinetics of GSK598809 combined with alcohol

No relevant effect of GSK598809 on ethanol pharmacokinetic parameters was observed. Regarding the effects of alcohol on GSK598809 pharmacokinetic parameters, an average 15% increase in AUC_∞ of GSK598809 (ratio of LS geometric means 1.15; 90% confidence interval 1.02/1.30) and an average 9% decrease in C_{max} of GSK598809 (ratio of LS geometric means 0.91; 90% confidence interval 0.83/1.00) was observed after administration of GSK598809 combined with alcohol compared to GSK598809 alone. Other parameters were roughly similar compared to GSK598809 alone (see table 2).

Pharmacodynamics of alcohol

Following alcohol infusion, a statistically significant decrease in adaptive tracking and smooth pursuit eye movements and increase in body sway were

observed compared to placebo, but there were no effects on saccadic peak velocity, inaccuracy or reaction time (see table 3 and figures 4 to 7). Clear increases in the feeling of being drunk were noted. In addition, there was some decrease in alertness on the VAS Bond & Lader scales, compared with placebo (see table 4 and figure 8). Alcohol did not demonstrate any clear effect on VVLT performance (see table 5).

Pharmacodynamics of GSK598809

Following administration of GSK598809, transient increases in serum prolactin were observed (see figure 9). Peak prolactin levels, which increased much more in females than in males ($p < 0.0001$), were reached roughly 3 hours after study drug administration and normalized within 12 hours. Administration of GSK598809 also caused a decrease in adaptive tracking performance, which was maximal between 2 and 6 hours after dose administration (see table 3 and figure 6). No statistically significant effects were observed on any of the other pharmacodynamic parameters (see tables 3 to 5 and figures 4, 5, 7 and 8).

Pharmacodynamics of GSK598809 combined with alcohol

Co-administration of GSK598809 and alcohol resulted in additive effects on several pharmacodynamic parameters, compared to either treatment alone (see tables 3 to 5 and figures 4 to 8). While the effects of administration of GSK598809 alone or alcohol alone on saccadic eye movements did not reach statistical significance, co-administration of GSK598809 and alcohol resulted in a significant impairment. No significant supra-additive effects were found on any of the pharmacodynamic parameters, except a small increase in saccadic reaction time (see table 3) and a small decrease in delayed word recall on the VVLT (see table 5).

DISCUSSION

The present study was performed to evaluate the pharmacokinetics and central nervous system (CNS) effects of single oral doses of 175 mg of the novel dopamine D_3 receptor antagonist GSK598809 in healthy volunteers and possible interactions with alcohol. Within the present group of healthy volunteers, single doses of GSK598809 were generally well tolerated. The most frequent adverse effects were mild headache, dizziness, somnolence, nausea and vomiting. GSK598809 did not induce any significant extrapyramidal symptoms. Mild short-lasting akathisia was reported spontaneously once after administration of GSK598809, although this was not verified objectively by the Barnes Akathisia Rating Scale, when this was performed according to protocol. Plasma concentration of GSK598809 increased rapidly after oral administration (t_{max} of roughly 2 to 3 hours) and subsequently decreased in an apparent bi-exponential manner (terminal half life of roughly 20 hours). No effect of GSK598809 on the pharmacokinetics of alcohol was observed, but alcohol decreased C_{max} and increased the AUC of GSK598809 to a limited extent, which is not considered to be of any clinical significance.

The CNS effects of GSK598809 alone were limited to an elevation of serum prolactin and a small decrease in adaptive tracking performance, with a time course that corresponds well with the observed pharmacokinetics. This study represents the first use of this pharmacodynamic test battery to evaluate the effects of a selective dopamine D_3 antagonist in healthy volunteers. As a result, no data of other dopamine D_3 receptor antagonists are available for comparison with the effects of GSK598809. Antipsychotic drugs (dopamine D_2 receptor antagonists) have been evaluated extensively with this pharmacodynamic test battery (de Visser *et al.*, 2001; Liem-Moolenaar *et al.*, 2010a; Liem-Moolenaar *et al.*, 2010b; Liem-Moolenaar *et al.*, 2011), but differences in tissue expression of D_2 and D_3 receptors and differences in receptor affinity profiles of the various drugs significantly limit the comparison of their effects to those of GSK598809.

Prolactin secretion by the lactotroph cells of the pituitary gland is under inhibitory control by dopamine, released predominantly from tuberoinfundibular dopaminergic neurons, acting on lactotrophic dopamine D_2 receptors (Ben-Jonathan and Hnasko, 2001; Freeman *et al.*, 2000). Pharmacological blockade of dopamine D_2 receptors removes this inhibitory influence and subsequently increases prolactin levels. However, the role of dopamine D_3 receptor antagonism in the control of prolactin secretion is unknown. An autoradiographic study has demonstrated presence of D_3 receptors in the pituitary gland (Herroelen *et al.*, 1994), but the density was quite low and any possible role for dopamine D_3 receptors in the pituitary gland in endocrine function remains unclear. Alternatively, dopamine D_3 antagonism may cause prolactin elevation by acting at the level of the hypothalamus. The periventricular and arcuate nuclei of the hypothalamus constitute the origin of the tuberoinfundibular dopaminergic pathway, which projects to the median eminence, where dopamine is released into the hypophyseal portal vessels (Albanese *et al.*, 1986; Ben-Jonathan and Hnasko, 2001; Moore and Bloom, 1978). Hypothalamic expression of dopamine D_3 receptors has not yet been examined in full detail, but one study found no detectable levels in the arcuate nucleus, whereas the periventricular nucleus was not investigated (Gurevich and Joyce, 1999). Therefore, any possible effect of dopamine D_3 antagonism on the hypothalamus, leading to prolactin elevation, also remains unclear. Another theoretical possibility is that GSK598809 could be acting on extra-dopaminergic mechanisms of prolactin control. However, a more likely explanation is that, despite a greater than 100-fold selectivity for D_3 receptors over D_2 receptors, GSK598809 at doses of 175 mg might cause enough D_2 receptor antagonism to modestly increase prolactin secretion.

The increases in serum prolactin following GSK598809 administration were much larger in female volunteers than in male volunteers (see figure 9). Similar gender differences in prolactin levels have been previously demonstrated after administration of typical antipsychotic drugs (Kuruvilla *et al.*, 1992; Meltzer and Fang, 1976; Meltzer *et al.*, 1983; Smith *et al.*, 2002; Wode-Helgodt *et al.*, 1977) and atypical antipsychotic drugs (Grunder *et al.*, 1999; Kinon *et al.*, 2003; Yasui-Furukori *et al.*, 2010), which have been attributed to an enhanced responsiveness of lactotrophs to prolactin-releasing stimuli by females, compared to males, due to the effects of estrogens (Ben-Jonathan and Hnasko, 2001; Buckman and Peake, 1973; Buckman *et al.*, 1976; PETty, 1999).

The other pharmacodynamic tests used in this study measure complex CNS functions. The neurophysiological and neurochemical mechanisms underlying these CNS functions have not yet been fully characterized, but are likely to involve multiple neurotransmitter receptor systems. The decrease in adaptive tracking performance after administration of GSK598809 indicates slight impairment in visuo-motor performance. Similar impairments in adaptive tracking performance have also been observed after administration of single doses of antipsychotic drugs (dopamine D_2 antagonists) such as haloperidol (Liem-Moolenaar *et al.*, 2010a) and risperidone (Liem-Moolenaar *et al.*, 2011) in healthy volunteers. However, unlike haloperidol and risperidone, GSK598809 did not affect smooth pursuit and saccadic eye movements, memory performance or any of the visual analogue scales. This clearly demonstrates the pharmacological distinctions between GSK598809 and antipsychotic drugs, but it is not necessarily an argument for D_3 receptor selectivity, since most antipsychotic drugs affect other neurotransmitter systems in addition to D_2 receptors. Recently, however, we examined the novel selective dopamine D_2 receptor antagonist JNJ-37822681 in healthy volunteers using similar pharmacodynamic tests (te Beek *et al*, 2011). Single oral doses of 15 mg JNJ-37822681 caused a reduction in adaptive tracking performance of about 2%, comparable to 175 mg doses of GSK598809. Also, this dose of JNJ-37822681 caused about 60% D_2 receptor occupancy and produced prolactin elevations of more than 700%, much larger than the 117% increase found with GSK598809 in this study. JNJ-37822681 also impaired saccadic and smooth pursuit eye movements, which were unaffected by GSK598809. Although these indirect comparisons have their limitations, they provide at least some support for the *in vivo* selectivity of GSK598809 for dopamine D_3 receptors.

In addition to obtaining a dopamine D_3 receptor-mediated profile of CNS effects, our study was specifically designed to evaluate potential pharmacokinetic and pharmacodynamic interactions between GSK598809 and alcohol. An intravenous alcohol clamping paradigm was used to achieve pseudo-steady state levels of alcohol, which produced clear and expected CNS effects, similar to previously reported results of this alcohol clamping paradigm (Zoethout *et al.*, 2008; Zoethout *et al.*, 2009). Co-administration of GSK598809 with intravenous alcohol levels at pseudo-steady state was generally well tolerated. However, somnolence and fatigue were reported more frequently, compared with the other treatments. Mild akathisia was reported spontaneously once, which was not verified objectively by the Barnes Akathisia Rating Scale, similar to the event after administration of GSK598809 alone. Co-administration of GSK598809 and alcohol generally produced additive CNS effects, without clear signs of supra-additive amplification of the effects of each treatment alone. Both GSK598809 and alcohol caused slight impairments of saccadic eye movements that failed to reach statistical significance by themselves, but the combination clearly differed from placebo. There was a small supra-additive increase in saccadic reaction time (see table 3) and there were also some indications that memory might be affected more by the combination than by each drug individually. These findings suggest that caution may be needed in the use of GSK598809 in individuals who consume alcohol moderately or excessively, although the effects will probably be dominated by alcohol.

In conclusion, the present study demonstrates elevation of serum prolactin and a small decrease in adaptive tracking performance after administration of the novel selective dopamine D_3 receptor antagonist GSK598809 within a small group of healthy volunteers. An interaction with intravenous alcohol infusion at pseudo-steady state was demonstrated, resulting in a decreased C_{max} and increased AUC of GSK598809 and mainly additive effects on several CNS parameters. Although somnolence and fatigue were reported more frequently, the combination was generally well tolerated by healthy volunteers.

FIGURE 1 STUDY DESIGN

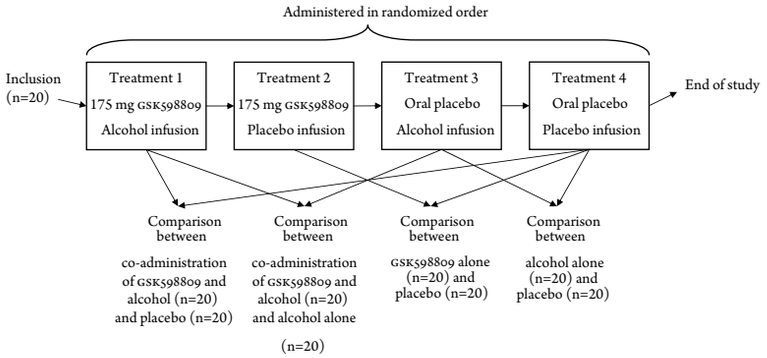

FIGURE 2 SERUM ALCOHOL LEVELS AFTER INTRAVENOUS ALCOHOL INFUSION

Starting at t = -0.5 hours and continuing until t = 4.5 hours, in combination with oral administration (at t = 0 hours) of GSK598809 (open circles) or placebo (closed circles). Means are presented with standard deviations as error bars.

FIGURE 3 PLASMA CONCENTRATIONS OF GSK598809 AFTER ORAL ADMINISTRATION

At t = 0 hours, in combination with intravenous alcohol infusion (open circles) or placebo infusion (closed circles) starting at t = -0.5 hours and continuing until t = 4.5 hours. Means are presented with standard deviations as error bars.

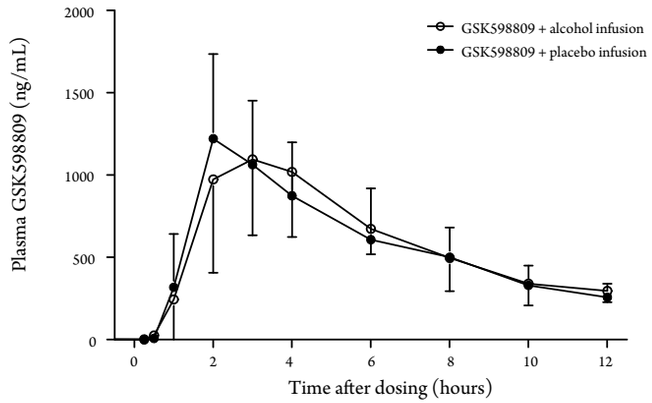

FIGURE 4 TIME COURSE OF SMOOTH PURSUIT EYE MOVEMENTS

Following administration of gsk598809 capsules combined with alcohol infusion. Least square means are presented with 95% confidence intervals as error bars.

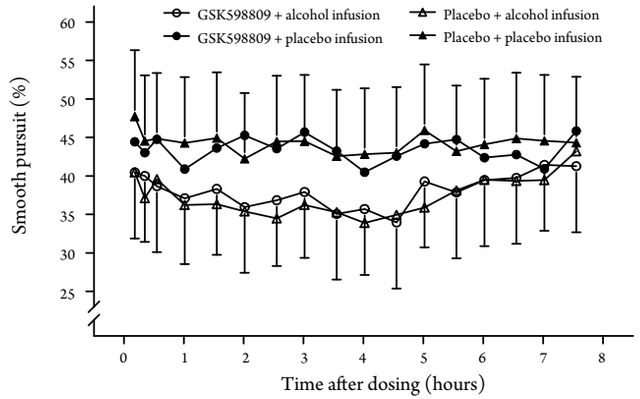

FIGURE 5 TIME COURSE OF SACCADIC PEAK VELOCITY

Following administration of GSK598809 capsules combined with alcohol infusion. Least square means are presented with 95% confidence intervals as error bars.

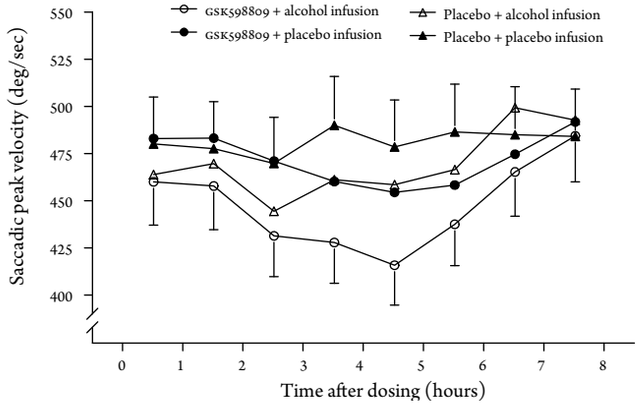

FIGURE 6 TIME COURSE OF ADAPTIVE TRACKING PERFORMANCE

Following administration of GSK598809 capsules combined with alcohol infusion. Least square means are presented with 95% confidence intervals as error bars.

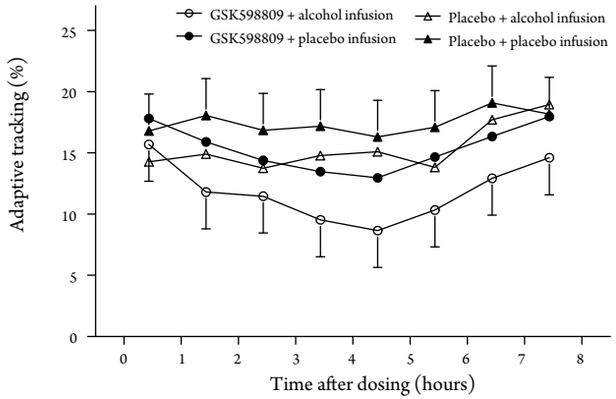

FIGURE 7 TIME COURSE OF BODY SWAY

Following administration of GSK598809 capsules combined with alcohol infusion. Least square means are presented with 95% confidence intervals as error bars.

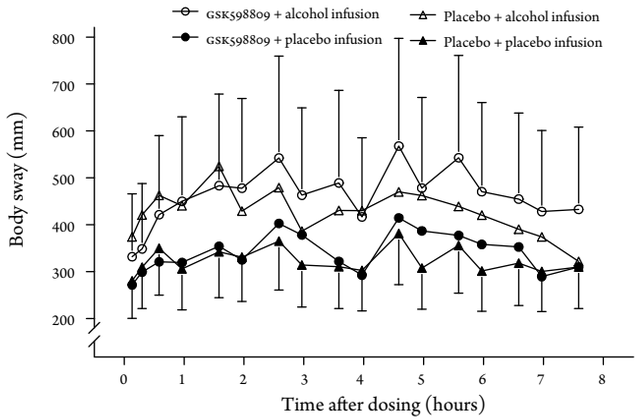

FIGURE 8 TIME COURSE OF ALERTNESS (VISUAL ANALOGUE SCALES OF BOND & LADER)

Following administration of GSK598809 capsules combined with alcohol infusion. Least square means are presented with 95% confidence intervals as error bars.

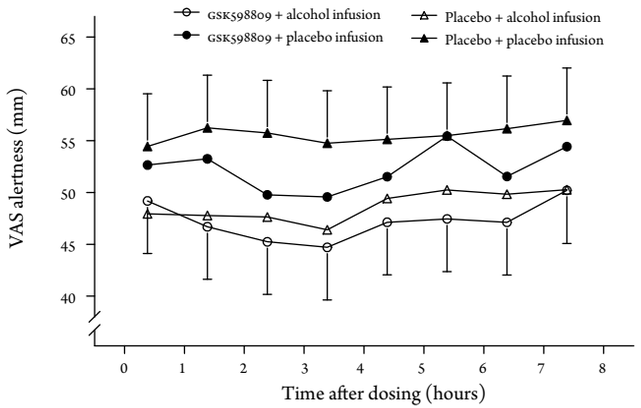

FIGURE 9 TIME COURSE OF SERUM PROLACTIN IN FEMALE (LEFT PANEL) AND MALE SUBJECTS (RIGHT PANEL)

Following administration of GSK598809 capsules combined with alcohol infusion. Means are presented with standard deviations as error bars.

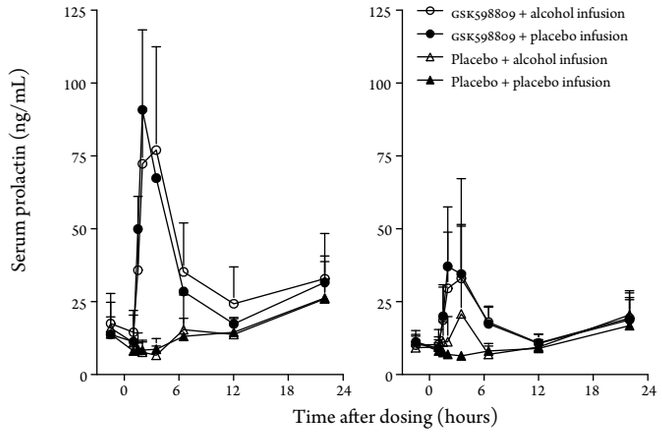

TABLE 1 SUMMARY OF COMMON ADVERSE EVENTS, REPORTED BY TWO SUBJECTS OR MORE

Incidence is based on the number of subjects, not the number of events.

Adverse event	**Placebo n = 19**	**Alcohol n = 20**	**GSK598809 n = 19**	**GSK598809 + Alcohol n = 19**
Headache	6 (32%)	9 (45%)	5 (26%)	7 (37%)
Somnolence	1 (5%)	4 (20%)	3 (16%)	11 (58%)
Dizziness	1 (5%)	6 (30%)	6 (32%)	5 (26%)
Akathisia	0	0	1 (5%)	1 (5%)
Feeling drunk	0	7 (35%)	0	6 (32%)
Fatigue	3 (16%)	4 (20%)	1 (5%)	7 (37%)
Infusion site pain	0	3 (15%)	0	2 (11%)
Catheter site related reaction	0	1 (5%)	1 (5%)	0
Nausea	0	1 (5%)	3 (16%)	3 (16%)
Vomiting	0	1 (5%)	4 (21%)	0
Dry mouth	0	0	0	2 (11%)
Upper respiratory tract infection	0	2 (10%)	0	0
Dysmenorrhoea	1 (5%)	0	0	1 (5%)
Oropharyngeal discomfort	1 (5%)	0	0	1 (5%)
Skin reaction	1 (5%)	1 (5%)	0	0

TABLE 2 PHARMACOKINETIC PARAMETERS OF GSK598809 WITH AND WITHOUT CO-ADMINISTRATION OF ALCOHOL

Data are presented as geometric means (with coefficient of variation), except t_{max} which is presented as median (with range). Note: n = 19 for all calculated values, except t½ and AUC_{∞} of GSK598809 alone (n = 11) and combined with alcohol (n = 15), because these parameters could not be calculated reliably in 8 subjects and 4 subjects, respectively.

Parameter	**GSK598809**	**GSK598809 + alcohol**
C_{max} (ng/mL)	1320 (39)	1190 (39)
t_{max} (h)	2.07 (2.0-6.05)	3.03 (2.00-7.87)
AUC_{0-t} (ng.h/mL)	14000 (28)	15700 (27)
AUC_{∞} (ng.h/mL)	14000 (32)	16600 (23)
Terminal half life (h)	19.3 (33)	21.6 (27)

TABLE 3 NEUROPHYSIOLOGICAL EFFECTS OF ADMINISTRATION OF ALCOHOL ALONE, GSK598809 ALONE AND CO-ADMINISTRATION OF GSK598009 AND ALCOHOL

Treatment differences in least square means are shown with statistically significant results indicated in bold.

Parameter	Alcohol compared with placebo	GSK598809 compared with placebo	GSK598809 + alcohol compared with placebo	GSK598809 + alcohol compared with alcohol alone	Supra-additive effects
Prolactin (ng/mL)					
Contrast	5.33%	**118.4%**	**113.1%**	**102.3%**	-7.35%
95% CI	-6.17/18.25%	**4.49/145.1%**	**89.74/139.3%**	**80.26/127.1%**	-21.3/9.10%
p-value	0.3711	**≤0.0001**	**≤0.0001**	**≤0.0001**	0.3525
Saccadic peak velocity (deg/sec)					
Contrast	-2.53%	-1.98%	**-7.15%**	**-4.73%**	-2.81%
95% CI	-5.01/0.01%	-4.45/0.57%	**-9.51/-4.72%**	**-7.18/-2.22%**	-6.30/0.80%
p-value	0.0505	0.1239	**≤0.0001**	**0.0005**	0.1229
Saccadic inaccuracy (%)					
Contrast	-0.23%	3.96%	**10.17%**	**10.42%**	6.21%
95% CI	-8.67/9.00%	-4.82/13.56%	**0.79/20.42%**	**0.97/20.75%**	-6.34/20.45%
p-value	0.9592	0.3805	**0.0334**	**0.0306**	0.3405
Saccadic reaction time (sec)					
Contrast	2.51%	2.09%	**9.20%**	**6.53%**	**4.35%**
95% CI	-0.43/5.54%	-0.83/5.09%	**6.05/12.44%**	**3.43/9.72%**	**0.11/8.76%**
p-value	0.0937	0.1584	**≤0.0001**	**≤0.0001**	**0.0443**
Smooth pursuit (%)					
Contrast	**-6.9**	-0.9	**-6.1**	0.8	1.7
95% CI	**-10.1/-3.7**	-4.1/2.3	**-9.3/-2.9**	-2.4/4.0	-2.9/6.2
p-value	**≤0.0001**	0.5930	**0.0004**	0.6210	0.4674
Adaptive tracking (%)					
Contrast	**-2.0**	**-2.0**	**-5.6**	**-3.5**	-1.5
95% CI	**-3.7/-0.3**	**-3.7/-0.3**	**-7.3/-3.9**	**-5.2/-1.8**	-3.9/0.9
p-value	**0.0207**	**0.0227**	**≤0.0001**	**0.0001**	0.2099
Body sway (mm)					
Contrast	**31.83%**	4.80%	**41.31%**	7.18%	2.27%
95% CI	**9.96/58.06%**	-12.6/25.70%	**17.69/69.67%**	-10.7/ 28.67%	-21.0/32.33%
p-value	**0.0035**	0.6066	**0.0004**	0.4493	0.8618

TABLE 4 VISUAL VERBAL LEARNING TEST (VVLT) RESULTS AFTER ADMINISTRATION OF ALCOHOL ALONE, GSK598809 ALONE AND CO-ADMINISTRATION OF GSK598009 AND ALCOHOL ON THE
Treatment differences in least square means are shown with statistically significant results indicated in bold.

Parameter	Alcohol compared with placebo	GSK598809 compared with placebo	GSK598809 + alcohol compared with placebo	GSK598809 + alcohol compared with alcohol alone	Supra-additive effects
Immediate recall 1st trial					
Contrast	-0.3	0.3	-0.8	-0.5	-0.8
95% CI	-1.6/1.1	-1.1/1.7	-2.1/0.6	-1.8/0.8	-2.7/1.1
p-value	0.6812	0.6725	0.2516	0.4554	0.4115
Immediate recall 2nd trial					
Contrast	-1.3	-0.1	-1.3	-0.0	0.1
95% CI	-2.8/0.3	-1.7/1.5	-2.9/0.2	-1.6/1.5	-2.1/2.3
p-value	0.1047	0.8822	0.0970	0.9640	0.9408
Immediate recall 3rd trial					
Contrast	-1.1	-1.0	**-2.7**	-1.6	-0.6
95% CI	-2.9/0.7	-2.8/0.8	**-4.5/-1.0**	-3.4/0.1	-3.2/1.9
p-value	0.2210	0.2702	**0.0034**	0.0704	0.6206
Delayed recall					
Contrast	-9.90%	11.31%	**-25.5%**	-17.3%	**-25.7%**
95% CI	-26.6/10.65%	-9.44/36.80%	**-39.4/-8.42%**	-32.7/1.56%	**-44.5/-0.60%**
p-value	0.3135	0.3020	**0.0061**	0.0692	**0.0456**
Word recognition (correct)					
Contrast	-0.82%	2.24%	-8.62%	-7.87%	-9.88%
95% CI	-12.1/11.91%	-9.49/15.48%	-19.1/3.22%	-18.3/3.95%	-24.1/6.97%
p-value	0.8923	0.7169	0.1436	0.1790	0.2288
Word recognition (incorrect)					
Contrast	9.81%	15.24%	39.26%	26.82%	10.05%
95% CI	-24.6/59.91%	-21.9/70.03%	-4.69/103.5%	-12.3/83.41%	-35.6/88.10%
p-value	0.6193	0.4670	0.0855	0.2017	0.7212
Reaction time (correct)					
Contrast	1.97%	1.72%	0.54%	-1.40%	-3.07%
95% CI	-4.70/9.11%	-4.98/8.90%	-6.08/7.64%	-7.85/5.50%	-11.9/6.70%
p-value	0.5649	0.6172	0.8736	0.6775	0.5176

TABLE 5 VISUAL ANALOGUE SCALES (VAS) RESULTS AFTER ADMINISTRATION OF ALCOHOL ALONE, GSK598809 ALONE AND CO-ADMINISTRATION OF GSK598009 AND ALCOHOL
Treatment differences in least square means are shown with statistically significant results indicated in bold.

Parameter	**Alcohol compared with placebo**	**GSK598809 compared with placebo**	**GSK598809 + alcohol compared with placebo**	**GSK598809 + alcohol compared with alcohol alone**	**Supra-additive effects**
VAS alertness (mm)					
Contrast	**-6.9**	-3.3	**-8.4**	-1.5	1.9
95% CI	**-11.4/-2.4**	-7.9/1.2	**-12.9/-3.9**	-6.0/3.0	-4.5/8.2
p-value	**0.0031**	0.1428	**0.0005**	0.5134	0.5574
VAS calmness (mm)					
Contrast	-1.5	-0.3	-0.9	0.6	0.9
95% CI	-3.8/0.8	-2.6/2.0	-3.2/1.4	-1.7/2.9	-2.4/4.2
p-value	0.1911	0.7964	0.4288	0.6024	0.5820
VAS mood (mm)					
Contrast	-2.0	-0.9	-0.9	1.1	2.0
95% CI	-5.0/0.9	-3.9/2.1	-3.9/2.1	-1.9/4.1	-2.2/6.2
p-value	0.1761	0.5537	0.5415	0.4542	0.3442
VAS alcohol effects (mm)					
Contrast	**23.1**	2.1	**24.6**	1.5	-0.6
95% CI	**13.4/32.8**	-7.6/11.8	**14.9/34.3**	-8.2/11.2	-14.3/13.1
p-value	**≤0.0001**	0.6650	**≤0.0001**	0.7588	0.9280

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