MEASUREMENT OF DRUG ACTION IN MAN:
PSYCHOMETRIC ASPECTS OF ANTIHISTAMINES

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Submitted in accordance with the requirements
for the degree of
Doctor of Philosophy

University of Surrey
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Submitted November 1999

The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others.

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ABSTRACT

The use of antihistamines (AHs) has until recently been associated with a number of undesirable side effects, the most troublesome of which is sedation. There are two aspects to sedation. The first, an objectively determined measure based on the results of psychometric tests from controlled trials, and the second, the subject’s response to the administration of a drug. Since AHs are largely used in ambulant patients, a complete evaluation of sedation should be performed through standardised objective tests, shown to be sensitive to the central effects of AHs and reliable ratings of subjective experiences. A critical review of the literature on the experimental studies with AHs revealed that the traditional AHs had a greater propensity to produce adverse central nervous system (CNS) effects, whereas the so-called second generation AHs were generally less impairing when administered within their recommended ‘dose window’. A similar review of the clinical literature surveying subjective reports of sedation following the administration of AHs showed that the traditional AHs were perceived as more sedative than the second generation AHs.

On the basis of these findings, a series of controlled experiments in non-atopic volunteers investigated the effects of a number of second generation AHs on various aspects of cognitive functioning and psychomotor performance. It is concluded that the second generation AHs have a lesser effect with respect to objective indices of sedation when compared to their predecessors, and that fexofenadine, has a claim to be the first truly non-sedating antihistamine as there is no objective evidence of CNS effects.

The identification of an antihistamine, devoid of adverse CNS activity regardless of the administered dose, highlights the need for the introduction of a ‘third generation’ of AHs.
In memory of my father, who would have been very proud of this achievement.
AKNOWLEDGMENTS

Firstly, I would like to thank Professor Ian Hindmarch for giving me the opportunity to undertake this PhD whilst under his employment.

I am also grateful to Professor Hindmarch for his supervision, advice and guidance on the preparation of this thesis.

I would like to thank the staff and students of the HPRU, who have assisted in the experimental work included in this thesis. I am especially grateful to Mrs Susan Kimber for her assistance and guidance with the statistical analyses of the data presented in this thesis.

I am indebted to my family for their constant encouragement, patience and understanding during the preparation of this thesis. I would like to especially thank my husband for his encouragement and understanding, especially during the final months of the preparation of this thesis.
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GLOSSARY OF ABBREVIATIONS

ACT  Actigraphy
AFS  Awakening from Sleep
AHs  Antihistamines
ANOVA Analysis of Variance
b.d. Twice daily
BDZs  Benzodiazepines
BFW  Behaviour following Awakening
CFF  Critical Flicker Fusion
CFQ  Cognitive Failures Questionnaire
CGI  Clinical Global Impression
CIU  Chronic Idiopathic Urticaria
CNS  Central Nervous System
CRT  Choice Reaction Time
CTT  Compensatory Tracking Task
DS  Digit Span
EEG  Electroencephalograph
GAD  Generalised Anxiety Disorder
GP  General Practice
GTS  Getting to Sleep
HAM-A  Hamilton Anxiety Rating Scale
I  Impairment
IgE  Immunoglobulin E
IP  Information Processing
LARS  Line Analogue Rating Scales for Sedation
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<td>MESS</td>
<td>Milford-Epworth Sleepiness Scale</td>
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<td>MMT</td>
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<td>MRT</td>
<td>Motor Reaction Time</td>
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<td>MSLT</td>
<td>Multiple Sleep Latency Test</td>
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<tr>
<td>NI</td>
<td>No impairment</td>
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<td>o.d.</td>
<td>Once Daily</td>
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<td>OTC</td>
<td>Over the Counter</td>
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<td>PIR</td>
<td>Proportional Impairment Ratio</td>
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<td>PSR</td>
<td>Proportional Sedation Ratio</td>
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<td>QOS</td>
<td>Quality of Sleep</td>
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<td>Recognition Reaction Time</td>
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<td>RT</td>
<td>Reaction Time</td>
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<td>RTA</td>
<td>Road Traffic Accident</td>
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<td>SAR</td>
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<td>t.i.d.</td>
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CHAPTER 1: INTRODUCTION

1.0 Chapter Outline
This chapter discusses the context in which the present research was carried out. The term 'sedation' is defined and the importance of measuring sedation, which is commonly associated with the use of the traditional first generation antihistamines (AHs), is highlighted. A brief introduction to the history of AHs is given followed by background information on the second generation AHs investigated in this thesis. Finally the contents of the thesis are outlined.

1.1 Introduction and Rationale
AHs have found their greatest therapeutic role in the treatment of various allergic disorders, particularly in the treatment of seasonal and perennial allergic rhinitis, conjunctivitis and acute urticaria, conditions where histamine mediated increase in capillary permeability and itch play a major role (Advenier & Queille-Roussel 1989, Flowers et al 1986, Tarnasky & Van Arsdel 1990, Wood 1988). The AHs are valuable in the treatment of allergic dermatoses, angio-oedema and chronic urticaria, providing symptomatic relief of pruritus (Monroe 1990). Some of the effectiveness of the antipruritic effects may relate to the sedative effects of some of these compounds (Krause & Shuster 1983), although this has been questioned through the treatment of itching in atopic eczema using AHs with a low sedative profile (Doherty et al 1989). AHs are also effective in the control of ocular symptoms such as lacrimation and erythema, and they are sold over the counter either as sole entities or in combination preparations for the treatment of the 'common cold' (West et al 1975). Much research has been conducted in to the controversial role of the H\textsubscript{1} receptor antagonists in the treatment of asthma and in
this indication, the AHs seem to be of limited value (Holgate 1994, Van Ganse et al 1997).

In addition, due to their non-specificity, the traditional AHs give rise to numerous side effects, some of which are often used therapeutically.

The anticholinergic action provides a drying effect on the nasal mucosa and the pulmonary system, as well as decreased gastric motility. This characteristic can be used beneficially to treat cholinergic excess associated with Parkinsonism and in drug-induced dyskinesia, by way of its central antagonism of acetylcholine actions (Peggs & Shimp 1995).

The anti-emetic effects, thought to be related to central muscarinic actions, decreased vestibular stimulation and labyrinthe function, or, by possibly affecting the chemoreceptor trigger zone, account for their use in motion sickness and vertigo (Norris 1988, Wood et al 1965). Some AHs directly suppress the cough reflex centre in the medulla, explaining their use as antitussives (Bryant & Lombardi 1993).

Recently, AHs have been indicated in the treatment of anxiety disorders and success has been demonstrated with hydroxyzine in this indication (Fererri et al 1995, Lader & Scotto, 1998, Shamsi & Hindmarch 1999).

Finally, it is worthy of note that antihistaminic properties are not limited to the AHs. There are other drugs such as tricyclic antidepressants (amitriptyline), and the calcium channel antagonists (cinnarizine) which possess antihistaminic effects as part of their pharmacological profile. However, this thesis is not concerned with other drug classes or indeed the use of these compounds for the treatment of various disorders in clinical practice, but is mainly concerned with the AHs and their potential to cause cognitive and psychomotor impairment.
The use of AHs has until recently been associated with a number of undesirable side effects, the most troublesome of which is sedation (Goetz et al 1991, Hindmarch & Shamsi 1999, Matilla et al 1986). The somnolence produced by the first generation AHs may be welcomed by those who use them as sedatives or perhaps by individuals with allergic disorders who suffer from intolerable pruritus (Simons 1996). However, excessive daytime sedation can disrupt the abilities necessary for the safe performance of the cognitive and psychomotor tasks of everyday life and thus increase the risk of accidents (Brookhuis et al 1993, Nicholson & Stone 1986, Rombaut et al 1989). In addition, excessive sedation is counter-therapeutic and reduces patient compliance and consequently the efficacy and utility of these AHs in clinical use (Pechadre et al 1991).

In order to overcome the sedation, some physicians recommend giving these older $H_1$ receptor antagonists at bedtime, because $H_1$ blockade may be maintained the next morning and somnolence is of no concern during the night (Simons 1996).

Unfortunately, the morning after taking an $H_1$ antagonist at bedtime, peripheral $H_1$ blockade may not persist and the adverse CNS effects may not have always disappeared (Passalacqua et al 1996, Simons 1996).

As a result of their widespread OTC availability, there are large numbers of ambulant patients using AHs. Sedation and cognitive impairment induced by the first generation AHs is an important factor to consider, especially since most of the OTC AHs are of the first generation type. A survey of hay fever sufferers found that more than half (54%) self medicated with OTC drugs and a third of these patients experienced drowsiness because of their therapies (Richards et al 1992).

It would therefore seem essential that any treatment maintains the integrity of the cognitive system so as to protect the ambulant patient from drug-induced accidents, particularly in those who may be driving motor vehicles and those working in risk-prone
domestic or industrial environments (Ramaekers et al 1992a, Sherwood & Hindmarch 1993). Furthermore, it is imperative that appropriate methods and measures are identified to discriminate and differentiate between AHs which do not produce sedation from those with which there is no evidence of sedation when recommended daily doses are ingested and those which are inherently sedative regardless of the dose administered.

1.2 Sedation

The term 'sedation' is generally used to describe depressant effects on the CNS. An inspection of even the most recent research reports reveals that there is no general agreement on the meaning of 'sedation' as applied to AHs.

Matilla et al (1986) report 'sedation of an unpleasant character' referring to a subjectively assessed loss of alertness. Nicholson and Stone (1986) write that 'impaired performance may be a non-specific effect of sedation'. Sedation was equated with drowsiness and was evaluated using subjective visual analogue scales (VAS) and EEG sleep latency tests. In fact, most investigators follow this approach and lump parameters of drowsiness together with measures of cognitive impairment, or alternatively the two kinds of CNS effects are included together on a continuum (Ahn & Barnett 1986, Hindmarch & Easton 1986, Nicholson & Stone 1986).

Within the context of this thesis however, the term 'sedation' is used to define a lowering of CNS activity which would be manifest as an impairment of superior cognitive functions such as attention, memory, sensorimotor co-ordination and psychomotor performance and which may or may not be associated with subjective feelings of tiredness, fatigue, drowsiness etc.

Until recent times, the history of pharmacotherapy has had a positive regard towards the term 'sedation'. It was towards the end of the 1970s that the sedation produced by
psychoactive drugs was recognised as a negative side effect. In 1972, the World Health Organisation (WHO) issued a caution against the use of psychoactive drugs liable to induce sedation in ambulant patients. This effect was recognised as a threat to patient safety as well as the determinant factor in reducing patient compliance. Consequently it became especially unacceptable that drugs with primary peripheral effects caused secondary sedation.

It appears therefore that the general interpretation of the term sedation indicates an adverse event and represents a source of impairment of normal daytime functioning, especially in the context of ambulant patients who may be driving cars or be involved in risk-prone industrial or domestic activities (Ramaekers et al 1992a). This concern becomes particularly important when it is considered that about 5% of drivers may use an antihistamine before driving (Starmer 1985). In an investigation examining the incidence of drug use among individuals killed in road traffic accidents (RTA) during a one year period, the adjusted culpability rate for AHs was 72% compared with 87% for alcohol, 90% for cannabinoids and 97% for tranquilisers and antidepressants (Warren et al 1981). Similarly, the incidence of fatalities associated with the use of psychoactive drugs in RTAs was assessed in the UK (Everest 1989). An overall incidence of 7.4% of drugs likely to affect the CNS was found in all RTAs and in 6.7% of those suffering fatal RTAs. AHs either as single entities or as combination products with antihistaminic activity were present in 1.76% of the fatal accidents. AHs were also more frequently detected (12%) in the bloods of accident involved drivers when compared to non-accident involved drivers (Jick et al 1981). Such findings highlight the need for restricting the use of the AHs especially those of the first generation type, and the development of AHs which are free of detrimental effects on cognitive and psychomotor functioning.
1.3 Histamine and Antihistamines - Historical Perspectives

Histamine was first identified as a potent vasoactive substance by Dale and Laidlaw in 1910. Over a period of seventy years, the knowledge of a much larger number of physiological activities has evolved. In 1931, in a series of experiments designed to demonstrate the actual release of histamine in association with the anaphylactic reaction, Watanabe (1931) noted differences in the histamine content of guinea-pig lung before and after shock. Dragstedt and Mead (1936) showed that the striking increase in the histamine content of the blood and lymph of dogs after anaphylaxis was sufficient to explain the shock and Code in 1937 noted that the amounts of histamine liberated in shocked guinea pigs were sufficient to produce anaphylactic symptoms. Blockade of many of the undesirable effects of histamine was first achieved by Bovet & Staub in 1937, when protection of guinea pigs against lethal doses of histamine, by a diethylamine derivative, was observed. Due to toxicity, clinical use was prevented and the search began for more acceptable agents.

By 1942, progress was being made in the direction of a relatively non-toxic antihistamine, although the first to have acceptable clinical use was Antergan, another diethylamine derivative. Neo Antergan (Pyrlamine maleate) soon followed in 1944, with diphenhydramine and tripelennamine discovered in the late 1940s. Since then literally hundreds of compounds have been tested for histamine blocking activity. Sixty years of intensive research was required to discover subclasses of the histamine receptor, through which, the wide-ranging activities of histamine are mediated. This discovery is attributed to Ash and Schild (1966), confirmed later by Black et al (1972) which led to a new therapeutic class of agents, the H₂ receptor antagonists.

The next step in the development of AHs was the introduction of H₁ blockers and the subsequent introduction of two distinct sub-classes of AHs, known as the older
'traditional' or 'classic' histamine antagonists and the newer 'non-sedating' histamine antagonists.

1.4 The Role of Histamine in Physiology

Histamine is a naturally occurring amine, produced by the decarboxylation of the amino acid, histidine, found in most body tissues, primarily mast cells and basophils. The physiological functions of histamine are suggested by its distribution in the body. Its presence in the surface membranes of the alimentary canal, respiratory tract and skin is in line with its role as a defence mechanism against foreign substances. As a mediator of the secretory process, histamine is also found in the gastric, intestinal, lacrymal and salivary glands.

Histamine also plays a role in regulating the micro-circulation in accordance with its presence in cells, which line small blood vessels. Histamine is released from the tissue mast cell and blood basophil, by an energy dependent mechanism, in response to immunological and non-immunological stimuli. The former involves the IgE mediated antigen-antibody reaction, whilst trauma, drugs and other substances frequently constitute non-immunological stimuli. Localised release leads to itching, redness and oedema of the skin, or bronchoconstriction of the lung, whilst generalised release may induce anaphylactic shock.

The actions of histamine arise from its interaction with specific receptors on various histamine responsive target tissues. The effects of histamine at the $H_1$ receptor include smooth muscle contraction, oedema which results from increased permeability of capillaries, flush and weal of the ‘triple response’ due to dilation of the capillaries, enhancement of respiratory mucus secretion and development of hypotension due to arterial dilation. The action of histamine at the $H_2$ receptor involves the increase in
gastric pepsin and acid secretion. A third histamine receptor, $H_3$ has recently been identified (Arrang et al 1983, Ishikawa & Sperelakis 1987), believed to have a role in the self-regulation of its own synthesis and release from nervous tissue, lung and skin.

1.5 Classification of the $H_1$-Receptor Antagonists

Unlike histamine, which has a primary amino group and a single aromatic ring, most $H_1$ antagonists have a tertiary amino group linked by a two or three atom chain to two aromatic constituents (figure 1.1). The classical AHs are basically related at their central portion by a substituted ethylamine core, a moiety also present in histamine itself.

**Figure 1.1 General formula of the classical AHs**

\[
\begin{array}{c}
\text{AR}_1 \\
\text{AR}_2 \\
\text{AR}_3
\end{array}
\]

The majority of these AHs are composed of one or two heterocyclic or aromatic rings ($\text{AR}_1$ & $\text{AR}_2$) connected by nitrogen, carbon or oxygen ($X$) to the ethylamine group. The nitrogen of this ethylamine group is tertiary, having two substituents ($R_1$ & $R_2$). It is the presence of multiple aromatic or heterocyclic rings and alkyl substitutes in these AHs that results in their lipophilic characteristics, thus explaining their CNS effects (Woodward 1990).

The nature of the linkage atom ($X$) has been used to categorise the classic AHs into six major classes. The various substitutions serve the purpose of modifying the characteristics of absorption and excretion as well as the side effect profile.

$X = O$, Ethanolamines e.g. Diphenhydramine, Clemastine
1.6 Postulated Mechanisms of Antihistamine-Induced Sedation

Numerous attempts to define the actual mechanism of antihistamine-induced sedation have been inconclusive. It is accepted however that histamine, like other biological amines, is a neurotransmitter in the brain with a role in the control of wakefulness and sedation (Nicholson et al 1985). Evidence to support this hypothesis lies in studies on the localisation of neuronal pathways and on the electrical responsiveness of the brain. Observations such as the desynchronisation of the EEG upon cerebrovascular injections of histamine (Wolff & Monnier, 1973), as well as the anatomical position of the ascending histaminergic pathway, projecting into the telecephalic regions suggest a role in arousal. This has been further confirmed by the circadian variation in the turnover of histamine in the brain, being in accordance with the maximum and minimum states of arousal (Nicholson et al 1985).

The underlying mechanisms by which CNS effects are caused by AHs is not precisely understood and is believed to be due to a number of factors. Penetration of the blood brain barrier to gain access to the CNS is a prerequisite before sedative side effects can occur (Meltzer 1990). The traditional AHs, due to their high lipophilicity, cross into the CNS without difficulty, and are therefore thought to be associated with sedative effects as a result of the interaction with the appropriate CNS receptor sites (Meltzer 1991, Simons 1989). Accordingly, the newer, second generation AHs with the hydrophilic
characteristics and greater molecular size (>90Da) do not penetrate the CNS and within their recommended doses, appear to be free from adverse CNS effects (Kaliner 1992, Simons & Simons 1991).

A second theory suggests that greater central versus peripheral H₁ affinity may account for the sedative activity of the traditional AHs (Le Fur et al 1981, Rose et al 1982, Uzan et al 1979). An alternative explanation for the sedation produced by the first generation is the slower association/dissociation of the H₁ receptor antagonist to and from the H₁ receptor (Wiech & Martin 1982, Timmerman 1999). Finally it has been proposed that the inhibition of N-methyl transferase may play a role in producing sedation with the traditional AHs (Netter & Bodenschatz 1967), through which increased concentration of histamine would become available to block central cholinergic, α-adrenergic or serotonin receptors, thereby producing effects which may be synergistic to the histaminic effects.

1.7 Second Generation Antihistamines

The development and introduction of the second generation of AHs has been a major step towards achieving the ideal qualities of an antihistamine, given that they should be non-sedating, have a rapid onset of action, provide 24 hour relief of histamine mediated symptoms, employ a single daily dosage regimen and have high affinity for H₁ receptors, but not so high as to preclude performance of skin tests several weeks after discontinuation (Simons & Simons 1988).

H₁-receptor antagonists differ considerably from each other in their pharmacokinetics and pharmacodynamics, and an understanding of these differences is essential for optimal usage of these medications (Simons 1990). Maximum antihistaminic effects of the H₁-receptor antagonists continue for hours after peak concentrations have been achieved. Due to their reversible and competitive inhibition, they should be given before
an anticipated exposure to allergen and subsequent allergic reaction, in order to enable the preferential binding to the H₁ receptors in the tissue before the agonist does (Bernstein 1993). Even when serum concentrations of H₁-receptor antagonists have declined to the lowest limits detectable, significant antihistaminic effects persist, probably because of the presence of the H₁-antagonist and/or its active metabolite(s). They are generally well absorbed when administered orally. They have extremely variable serum elimination half-life values, ranging from hours to days (cetirizine, 7 hours; astemizole, 9.5 days). Except for cetirizine, all of the currently available second generation AHs are metabolised extensively by the hepatic cytochrome P450 system. The maximum antihistaminic effect of these medications occurs several hours later than the peak serum concentrations and the duration of the antihistaminic effect is much longer than would be predicted from the serum elimination half-life values (Gonzalez & Estes 1998). The relative incidence of anticholinergic and CNS adverse effects caused by these medications is similar to that produced by placebo when they are administered at the manufacturer's recommended dose (Haria et al 1994, Hindmarch et al 1999; McTavish et al 1990, Richards et al 1984, Spencer et al 1993, Wiseman & Faulds 1996). The chemical structures of a number of these second generation AHs are presented in figure 1.2.
Figure 1.2 The chemical structures of a number of second generation \( H_1 \) receptor antagonists

- Cetirizine
- Astemizole
- Ebastine
- Fexofenadine
- Loratadine
- Mizolastine
- Terfenadine
**Ebastine**

Ebastine is a selective and long acting H1-receptor antagonist, chemically related to terfenadine. Ebastine is well absorbed and extensively converted to its active carboxylic acid metabolite, carebastine with peak plasma concentrations of the metabolite occurring 3-4 hours following oral administration and lasting up to 24 hours (Wiseman & Faulds 1996). In healthy human volunteers, ebastine significantly inhibited histamine-induced weal and flare compared with placebo (Buchmeier et al 1994, Vincent et al 1988a).

Onset of antihistaminic action was evident within 1 to 3 hours of administration, peaked between 3-12 hours and was sustained for at least 24 hours (Vincent et al 1988a). As regards the CNS depressant effects of ebastine, clinical studies have demonstrated the lack of impairments when administered at its recommended therapeutic dose of 10mg daily (Brookhuis et al 1993, Hopes et al 1992, Mattila et al 1992, Mattila et al 1993, Vincent et al 1988b). However, evidence exists to support the notion that ebastine may cause impairments in cognitive and psychomotor abilities when administered at doses above 10mg (Vincent et al 1988b, Barbanoj et al 1988).

**Cetirizine**

Cetirizine is the carboxylated derivative and principal metabolite of the potent first generation antihistamine hydroxyzine. Cetirizine is rapidly absorbed, reaching peak plasma concentration within one hour of administration, and has a terminal half-life of 7-11 hours. It possesses a potent and long lasting antihistaminic activity, peaking 4-8 hours after dosing and lasting up to 24 hours (Spencer et al 1993). Comparative studies indicate that cetirizine 10mg has a more rapid onset of antihistaminic action than terfenadine 60-120mg, loratadine 10mg, astemizole 10mg, chlorpheniramine 4mg and ebastine 10mg in healthy volunteers (Simons et al 1990). Clinical studies have clearly
demonstrated the lack of CNS impairments when cetirizine is administered at its recommended therapeutic dose of 10mg daily (Schweitzer et al 1994, Simons et al 1995, Simons et al 1996, Tharion et al 1994). However, a number of studies have demonstrated significant impairments following the administration of higher doses of cetirizine (Gengo & Gabos 1987, Nicholson & Turner 1998, Riedel et al 1990a).

**Fexofenadine**

Fexofenadine is the active metabolite of terfenadine and has been shown to possess potent antihistaminic activity in studies with healthy volunteers and symptomatic patients (Bernstein et al 1997, Simons & Simons 1997). Following oral administration, fexofenadine is rapidly absorbed reaching maximum concentration within 1-2 hours. Pharmacological effects occur within 1-2 hours and are sustained over a period of 24 hours (Simons & Simons 1997). Comparative studies indicate that fexofenadine has a much faster onset of action than loratadine (Simons & Simons 1997). As regards the CNS depressant effects of fexofenadine, clinical studies have clearly demonstrated the lack of impairments when fexofenadine is administered at doses up to 240mg (Hindmarch et al 1999, Nicholson & Turner 1999, Vermeeren & O’Hanlon 1998). In this respect, fexofenadine appears to be different from the other second generation AHs in that it is free of detrimental effects on aspects of performance and cognition even when administered at doses which are higher than the recommended clinically effective dose regimen. In addition, unlike its parent compound, fexofenadine is not associated with any cardiac side effects (Gonzalez & Estes 1998, Pratt et al 1997).
**Loratadine**

Loratadine is also a selective H₁-receptor antagonist, which lacks the CNS depressant effects when administered at its recommended daily dose of 10mg (Bradley & Nicholson 1987, Roth et al 1987). Loratadine is rapidly absorbed after single oral administration, with peak plasma concentrations occurring 1 to 1.5 hours after ingestion of 10-40mg doses (Haria et al 1994). Onset of antihistaminic action with loratadine occurs within the first hour and is sustained for 24 hours (Kassem et al 1988, Roman et al 1986). Direct comparison of single doses of various AHs in healthy volunteers revealed the following order of activity: cetirizine 10mg > terfenadine 120mg > terfenadine 60mg > loratadine 10mg > astemizole 10mg > chlorpheniramine 4mg > placebo (Simons et al 1990).

Within the recommended therapeutic dose, loratadine is free from CNS adverse effects, however the administration of higher doses of loratadine has been reported to cause CNS impairments (Bradley & Nicholson 1987, O’Hanlon 1988, Riedel et al 1990b, Roth et al 1987). While the doses which appear to be causing the sedation are higher than those recommended by the manufacturer, a powerful reduction in the histamine induced weal and flare response is only achieved with a 40mg dose of loratadine (Rihoux et al 1990), which is associated with significant CNS impairments.

**Terfenadine**

Terfenadine was the first second-generation antihistamine that became available clinically. It is well absorbed with peak plasma concentrations occurring one to two hours after drug administration (McTavish et al 1990). Terfenadine undergoes extensive first pass metabolism via the isoenzyme CYP3A of cytochrome P450 system to result in the formation of a major active metabolite, once referred to as the ‘acid-metabolite’ and now better known as fexofenadine (Gonzalez & Estes 1998, Simons 1990). Following a
single 60mg dose of terfenadine, maximum suppression (approaching 100%) of the weal response in healthy volunteers is evident after 4 hours and persists for 12 hours (Huther et al 1977). A single oral dose of 120mg has been shown to significantly inhibit the weal and flare response for up to 24 hours (Shall et al 1988). As regards CNS depressant activity, a large number of clinical studies has demonstrated the lack of either objectively measured or subjectively reported incidence of impairment with terfenadine (as assessed by a battery of valid, reliable and sensitive tests) at doses up to 600mg/day for up to 7 days (Betts et al 1984, Gaillard et al 1988, Kulshrestha et al 1978, Moskowitz & Burns 1988, Nicholson & Stone 1982).

The use of terfenadine has been restricted recently in the UK following the reports of potent cardiac side effects when terfenadine is administered concomitantly with cytochrome P450 system inhibitors such as the macrolide antibiotics (erythromycin) and antifungal drugs (ketoconazole) (Simons 1993).

1.8 Measuring Antihistamine-Induced Sedation

Having established that sedation produced as a result of antihistamine use is an unwanted (side) effect and that the accompanying sedation with a number of these AHs has serious implications in terms of safety for the patient, one needs to find ways to assess this sedation. There are two ways of assessing histamine-induced sedation.

Firstly, information about drug induced sedation can be gathered by asking the patient. This can be done either at regular time intervals during treatment as the patient visits their physician, or daily, by means of completing daily diary cards. Using this method, the questioning can be structured to varying degrees, from open, non-directive interviewing, to specific questioning using a set of potential effects. It is however clear that the response can be combined or verified by the opinion of the physician, as the
reported experience is entirely subjective both with regard to its possible presence and severity. Another disadvantage of using subjective reports is that they lack objective measurement of the reported experience. Inter-subject variability also reduces the quality of the results obtained.

Secondly, the possible sedative potential of an antihistamine can be investigated in a standardised fashion, using a battery of validated and reliable, sensitive objective tests in healthy volunteers, in which varying test times can be incorporated into the design and the effects of different doses can be investigated.

1.9 Thesis Outline

As a first step in identifying the extent to which sedation is produced by AHs, chapter 2 will investigate the extent of sedation produced by AHs in the healthy volunteers and chapter 3 will review the clinical literature. Based on this evidence, chapter 4 will detail the measures and methods chosen for the experimental work and the results of the experiments will be presented in three sections in chapter 5. Part one of chapter 5 will present the results of two experiments (1 & 2) in which the peripheral suppressing ability of a number of AHs were assessed and part two will present the results of four experiments (3-6) in which the effects of AHs on aspects of cognitive and psychomotor function were investigated in healthy volunteers. The final part of chapter 5 will present the results of an experiment which was conducted in patients within a general practice (GP) setting. The final chapter (chapter 6) will discuss the relevance of the findings and recommendations for future research.
CHAPTER 2: PSYCHOMETRIC ASSESSMENT OF SEDATION AND OTHER ASPECTS OF PSYCHOMOTOR FUNCTION IN EXPERIMENTAL STUDIES OF ANTIHISTAMINES IN HEALTHY VOLUNTEERS - A LITERATURE REVIEW

2.0 Chapter outline

This chapter presents a critical review of previous experimental research on the effects of AHs on measures of cognitive function and psychomotor performance in healthy volunteers. This review will aim to differentiate those AHs, which can claim to be completely free of sedation from those which are non-sedating when administered within their recommended dose regimen and those with obvious and pronounced sedative activity.

The present review concentrates only on psychometric assessments and takes no account of efficacy variables or other side effects, which may determine the clinical choice for use of a particular drug.

A secondary objective is the identification of those psychometrics which are reliable indicators of the sedative effects of AHs and therefore to be preferred when assessing the CNS profile of novel compounds.

2.1 Introduction

Chapter one presented an introduction to the AHs and highlighted that the administration of the first generation AHs is commonly associated with a number of undesirable CNS side effects, the most troublesome of which is sedation (Brookhuis et al 1993, Goetz et al 1991, Hindmarch & Shamsi 1999).
In this review, the term 'sedation' is used to define a lowering of CNS activity which would be manifest as an impairment of superior cognitive functions such as attention, memory, sensorimotor co-ordination and psychomotor performance and which may or may not be associated with subjective feelings of tiredness, fatigue, drowsiness etc (Hindmarch & Shamsi 1999).

As AHs are widely used for the treatment of allergic disorders such as seasonal allergic rhinitis (SAR), then such usage is mainly by ambulant patients including children, and any CNS effects could compromise performance and safety. Any psychometric evaluation of such potential sedative activity therefore requires the investigation of the effects of a given antihistamine on cognitive processes using a well-defined, valid and refined model of information processing.

2.1.1 Information processing

To measure the action of a particular drug on human behaviour, whether to assess the clinical change produced by drug treatment or to profile its pharmacodynamic activity requires reliable and valid ratings and measurement systems as well as pertinent methodologies and controls to enable comparison with other drugs in the same class.

To examine the ways in which the activity of psychoactive drugs can be measured on psychomotor performance, Hindmarch (1980) proposed a basic model of information processing. In this model, the human organism is regarded as an information processing system, where sensory information is processed and organised centrally, before being formed into motor response schemes, which are ultimately realized in behaviour.

Figure 2.1 presents a simple model of information processing adapted from Hindmarch (1980). The model isolates the major processes as separate mechanisms.
Figure 2.1 A model of information processing (adapted from Hindmarsh 1980)
within a linear system. Information from the environment is attended to and passed to higher cognitive mechanisms, where it is analysed and, if required, integrated with information from memory. A decision concerning appropriate response is then reached and the response output mechanisms activated. Although the major components of the model appear to be compartmentalised, they should not be perceived as discrete entities, but rather as a chain of events which are intrinsically linked through adaptive feedback mechanisms (Fairweather 1997). The level of processing of one stage may affect performance at a different level or in another modality; for example, if the sensory processes are in error, then any subsequent central and motor responses will consequently be deficient, although acquired knowledge, skill and experience may ultimately provide a correct interpretation.

A psychoactive compound has the potential to affect all these sensory, central and motor components of information processing via both direct and indirect mechanisms. It must be noted however that the effect of drugs on information processing can be inferred from changes observed in overt behaviour or task performance. Following a review of the literature, Hindmarch (1980) grouped the tests according to the psychological variables they were thought to affect.

For the purposes of the present literature review, the tests have been categorised by grouping together those tests measuring similar CNS ‘behaviours’ (table 2.1).
Table 2.1: Categories and codes for measures of performance

<table>
<thead>
<tr>
<th>Category</th>
<th>Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor Performance</td>
<td>A: Actual Car Driving, Simulated Car Driving</td>
</tr>
<tr>
<td>Psychomotor Speed</td>
<td>B: Choice Reaction Time, Simple Reaction Time</td>
</tr>
<tr>
<td>Sensorimotor Co-ordination</td>
<td>C: Adaptive Tracking, Critical Tracking, Continuous Tracking, Pursuit Rotor, Simulated Car Tracking, Visuo-Motor Co-ordination</td>
</tr>
<tr>
<td>CNS Arousal, Information Processing</td>
<td>D: Critical Flicker Fusion</td>
</tr>
<tr>
<td></td>
<td>E: Digit Symbol Substitution Task, Letter Cancellation, Visual Search Task</td>
</tr>
<tr>
<td></td>
<td>F: Grammatical/Logical Reasoning, Mental Arithmetic</td>
</tr>
<tr>
<td></td>
<td>G: Stroop Colour Test</td>
</tr>
<tr>
<td>Memory</td>
<td>H: Continuous Memory Task, Short Term Memory</td>
</tr>
<tr>
<td>Sensory Skills</td>
<td>I: Vigilance Task</td>
</tr>
<tr>
<td></td>
<td>J: Attention Task, Continuous Attention Task, Simulated Assembly Line Task</td>
</tr>
<tr>
<td></td>
<td>K: Dynamic Visual Acuity</td>
</tr>
<tr>
<td></td>
<td>L: Spatial Perception</td>
</tr>
<tr>
<td>Motor Ability</td>
<td>M: Dexterity Test, Finger Tapping, Glass Bead Picking Test, Pegboard</td>
</tr>
<tr>
<td>Physiological</td>
<td>N: Electroencephalograph (EEG), Continuous EEG, Evoked Potentials, Multiple Sleep Latency Test</td>
</tr>
<tr>
<td></td>
<td>O: Actigraphy</td>
</tr>
<tr>
<td>Subjective Ratings</td>
<td>P: Profile of Moods Scale, Stanford Sleepiness Scale, Visual Analogue Rating Scales</td>
</tr>
</tbody>
</table>
Several tests measure more than one aspect of performance and these have been categorised according to their most relevant feature. In addition to obtaining objective data, it is important that subjective views are also recorded. This is particularly true for CNS active drugs, where cognitive appraisals of a particular scenario could influence overall psychomotor and cognitive function. Although this subjective aspect is not represented as a separate entity within the model, there is an obvious cognitive aspect where the subject is required to interpret and respond to the question by comparing present experiences of sedation and general impairments with memories of prior exposure.

Figure 2.2 illustrates those aspects of psychological performance assessed using a particular test system. It is evident that AHs have been widely tested, using a range of psychometrics analogous to most aspects of human information processing and daily function, although the effects of AHs on memory are ill-defined and it has been demonstrated (Curran et al 1998, Hindmarch & Bhatti 1987, Hindmarch & Easton 1986, Peck et al 1975, Smith & Janowski 1984, Unchern et al 1986) that this aspect of information processing is not affected with AHs.

The choice of a particular psychomotor test and the knowledge of its limitations are central to the understanding of any effects found. Thus, thorough psychopharmacological assessment requires a range of tests to ensure that subtle or specific drug effects are not overlooked. The clear need is for chosen tasks to be representative of key, well-defined and accepted areas of cognition and psychomotor performance. Theoretically one should use a test battery where separate and conjoined aspects of performance are measured (Hindmarch 1980, Hindmarch & Shamsi 1999).
Figure 2.2: Categorisation of tests into the information processing model (adapted from Hindmarch 1980)

Psychomotor Performance
- A: Actual Car Driving
- Simulated Car Driving
- Simulated Car Tracking

Sensory
- E: Vigilance
- Attention, Spatial Perception

Central Processing
- C: Critical Flicker Fusion
- Mental Arithmetic
- Logical reasoning
- Visual Search task
- D: Memory

Sensorimotor Performance
- B: Reaction Time Tracking,
- Visuomotor Coordination

Motor
- F: Finger Tapping,
- Dexterity Test

Subjective
- H: VAS, POMS,
- SSS
A cursory review of the literature (Rombaut & Hindmarch 1994, Hindmarch & Shamsi 1999) reveals clearly that some ‘tests’ are more sensitive, valid and reliable than others, but it is also true that there is no single test that can satisfy all criteria in covering all aspects of human performance. A large number of trials has been carried out to investigate the central effects of AHs in asymptomatic subjects (Haria et al 1994, Hindmarch et al 1999, Hindmarch & Rombaut 1994, Hindmarch & Shamsi 1999, Mctavish et al 1990, Richards et al 1984, Hindmarch & Rombaut 1995, Spencer et al 1993, Wiseman & Faulds 1996). In assessing possible central effects of AHs, large numbers of tests have been employed. However, many of these tests are not valid indicators of CNS effects such as the kinaesthetic figural after effect (Gupta 1974), the speed of putting caps on ball point pens (Lahtinen et al 1978) and flying simulators (Kay 1995). A number of tests have not been shown to be reliable indicators of CNS activity, e.g. a time estimation procedures (Wittenborn et al 1976) and multiple limb coordination (Fleishman & Hempel 1956) and, it is difficult to reproduce the results of particular experimental investigations to confirm and validate results.

A number of steps can be taken to ensure the validity and reliability of an experiment, such as screening volunteers to ensure sensitivity to the sedative effects of AHs, prior to participation. In a study by Hindmarch & Easton (1986), twenty-one volunteers were screened for sensitivity to a loading dose of chlorpheniramine 12mg of which only nine volunteers showed a significant reduction in CFF scores and were thus eligible for participation. It was argued that if a novel antihistamine (mequitazine in this instance) did not show sedation in a group of known ‘antihistamine responders’, then it would be feasible to claim that mequitazine was a non-sedating antihistamine.

This approach may not always be feasible as it is not only time consuming but also adds to the general workload of the trial in terms of additional testing. More importantly the
effects of an acute antihistamine challenge may be attenuated on repeated administration. The simplest way of ensuring the validity of an experiment is the inclusion of a verum (positive control). By inclusion of a verum, the sensitivity of the test battery is guaranteed so long as the verum condition produces sedation as determined by the particular test in question. If following the use of a verum, effects are not obvious on an assessment measure, then it must be assumed that the test is insensitive and no credence can be given to any findings obtained in such an instance (Hindmarch & Shamsi 1999). Similarly, the reliability of an experiment is simply achieved by showing the verum condition producing the same results on the same tests on repeated administration (Parrott 1991a).

First generation AHs such as promethazine, hydroxyzine, clemastine and triprolidine have been commonly and consistently shown to impair performance on a wide range of tests (Alford et al 1989, Bateman & Rawlins 1984, Hindmarch et al 1999, Levander et al 1985, Mattila et al 1986, Rombaut et al 1991, Shamsi & Hindmarch 1999a, Shamsi & Hindmarch 1999b, Simons et al 1995, Vermeeren & O’Hanlon 1998). For this reason, they are frequently included in studies as positive internal controls, when investigating the central effects of AHs.

The present review focuses on studies using placebo and verum controls, as the inclusion of both conditions is of paramount importance for the interpretation of results. A previous review of this kind has been conducted by Rombaut & Hindmarch (1994) and Hindmarch & Shamsi (1999), however the findings of both previous reviews were only analysed to provide an impairment/no impairment ratio for each antihistamine. This was achieved by calculating the number of discrete tests with which an impairment was detected (I) together with the number of tests administered at the same time and in the same study protocol with which no impairment was reported (NI). The ratio of I/NI was
then calculated by dividing the former by the latter value, the result of which represented the likelihood that a given antihistamine would produce sedative effects. The more impairment observed with a drug, the greater would be the I/NI ratio. Conversely, little evidence of sedation or impairment of cognitive and psychomotor function would result in a value close to zero. In as much as this gave a working classification and allowed the AHs to be ranked according to their ability to impair performance, the ratio obtained did not reflect a true scenario, as the effects of all other AHs measured on the same tests were not taken into account. In other words, the effects of a particular antihistamine were considered in isolation and without reference to the properties of other AHs. Taking the properties of all AHs into account as a ‘common denominator’ permits more accurate inter-drug comparisons to be made.

The use of a database of all drugs in a particular therapeutic category to provide an index of overall drug activity is a useful way of ranking a particular drug with respect to all other similar substances and ensures a more representative way of comparing one drug with another.
2.1.2 Proportional Impairment Ratio (PIR)

The technique for calculation of a proportional ratio is adapted from that used in pharmacovigilance (Stather 1998). Proportional impairment ratio (PIR) calculates the effects of a particular antihistamine against all other AHs and rankings take into account both positive and negative findings. The calculation of PIR is explained in figure 2.3. The PIR shows whether the use of an antihistamine is associated with psychomotor impairments and if so, the extent of that impairment when compared to the effects of other AHs. The greater the PIR, the greater are the impairments associated with the use of that antihistamine. Conversely, an antihistamine with which there is no evidence of impairment when tested across a range of doses would have a PIR value of zero. AHs with detrimental effects, which become evident only when higher doses are administered, would have PIR values closer to zero than those which are associated with impairments regardless of the dose administered.

In addition to the calculation of the PIR value, it is important to calculate its statistical significance, which gives a measure of the confidence with which the PIR values can be used to rank the AHs as regards their potential to cause psychomotor impairments.

The statistical association for each PIR is calculated using the chi-squared test ($X^2$) on one degree of freedom with Yate’s correction (Hinton 1995). In the calculation of the $X^2$, if the cell frequencies are small, then the difference between the observed and expected frequencies will appear large and the $X^2$ will tend to be significant. This may result in a Type I error, which is the error of rejecting the null hypothesis when it is true. In order to compensate for this problem, the $X^2$ for every cell is reduced by 0.5 before it is squared, which results in a smaller calculated value of $X^2$, thus reducing the risk of a Type I error (Hinton 1995).
Figure 2.3 Calculation of a Proportional Impairment Ratio (PIR) for AHs

\[ PIR = \frac{a}{a + b} \text{ divided by } \frac{c}{c + d} \]

(As defined below)

<table>
<thead>
<tr>
<th></th>
<th>Impairment</th>
<th>No Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific antihistamine</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>All other AHs on the database</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

\(a, b, c\) and \(d\) represent a particular number of instances where individual psychometric tests have shown impairment or no impairment with a particular antihistamine.

In order to calculate a PIR for each antihistamine listed, two separate calculations were made. In the first instance, the number of tests with which impairments were detected with a specific antihistamine \(a\) was divided by the total number of times in which both impairments \(a\) and no impairments \(b\) were reported with the same compound \(a + b\) to provide an ‘impairment ratio’ for that specific antihistamine \(a/(a+b)\). Secondly, to calculate an ‘impairment ratio’ for all other AHs, the number of discrete tests with which impairments were detected when all other AHs were taken into account \(c\) was divided by the total number of times with which both impairments \(c\) and no impairments \(d\) were reported \((c+d)\).
The PIR for each specific antihistamine was subsequently calculated by the division of the ‘impairment ratio’ for the specific antihistamine by the ‘impairment ratio’ of all other AHs in the database.

2.2 Literature Review

A computer-assisted MEDLINE search was conducted to identify studies which reported the effects of AHs on cognitive function and psychomotor performance from placebo and verum controlled studies reported in published papers from January 1971 up to August 1999. MEDLINE search ensured that only studies published in peer reviewed journals meeting specific criteria for acceptance were included in the review. Search terms included histamine, H₁ receptor antagonists, antihistamines, psychomotor performance, cognitive function, psychometrics and specific drug names. The search was limited to studies performed in humans. Studies had to be placebo and verum controlled, performed in healthy asymptomatic volunteers, and of particular interest were studies using standardised, quantitative methods of defining both objective and subjective drug-induced effects of sedation, psychomotor performance and cognition. Studies using a parallel group design or those not employing a crossover design or where interaction with alcohol or other CNS substances was the primary variable and studies with children were excluded. A list of studies excluded with reasons for non-inclusion can be found in table 2.2. As well as publications, data have been also included from studies published in abstract format in peer-reviewed journals, so long as the study satisfied the inclusion criteria and the data were presented in a format that enabled the PIR analysis to be performed.
Table 2.2: A list of studies excluded from the review

<table>
<thead>
<tr>
<th>DRUG</th>
<th>OTHER TREATMENTS IN STUDY</th>
<th>REASON FOR EXCLUSION</th>
<th>NO OF STUDIES</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astemizole</td>
<td>Placebo</td>
<td>No verum</td>
<td>3</td>
<td>De Gier et al 1986, Dhorraintra et al 1986, Hindmarch &amp; Easton 1986,</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Parallel design</td>
<td>1</td>
<td>Moser et al 1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No verum</td>
<td>1</td>
<td>Kohl et al 1987, Seppala &amp; Savolainen 1982</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incomplete information</td>
<td>1</td>
<td>Rombaut et al 1989</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination treatment</td>
<td>1</td>
<td>Stanley et al 1996</td>
</tr>
<tr>
<td>Brompheniramine</td>
<td>Placebo</td>
<td>No verum</td>
<td>1</td>
<td>Millar &amp; Standen 1982</td>
</tr>
<tr>
<td></td>
<td>Placebo, Terfenadine,</td>
<td>No verum</td>
<td>2</td>
<td>Pechadre et al 1988, Rihoux &amp; Dupont 1987,</td>
</tr>
<tr>
<td>Clemastine</td>
<td>Placebo</td>
<td>No verum</td>
<td>1</td>
<td>Hindmarch 1976</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alcohol interaction</td>
<td>1</td>
<td>Franks et al 1979</td>
</tr>
<tr>
<td>DRUG</td>
<td>OTHER TREATMENTS IN STUDY</td>
<td>REASON FOR EXCLUSION</td>
<td>NO OF STUDIES</td>
<td>REFERENCES</td>
</tr>
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<td>------------------</td>
<td>---------------------------</td>
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<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>Placebo</td>
<td>Alcohol interaction</td>
<td>1</td>
<td>Franks et al 1978</td>
</tr>
<tr>
<td></td>
<td>Astemizole</td>
<td>Alcohol interaction</td>
<td>1</td>
<td>Hindmarch &amp; Bhatti 1987</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Placebo</td>
<td>Alcohol interaction</td>
<td>3</td>
<td>Baugh &amp; Calvert 1977, Hughes &amp; Forney 1964, Linoila 1973</td>
</tr>
<tr>
<td>Ebastine</td>
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<td>No verum</td>
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<td>Mattila et al 1993, Vincent et al 1988b</td>
</tr>
<tr>
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<td>Clemastine</td>
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<td>1</td>
<td>Hagermark et al 1985</td>
</tr>
<tr>
<td>Levocabastine</td>
<td>Placebo</td>
<td>No verum</td>
<td>1</td>
<td>Arriaga &amp; Rombaut 1990</td>
</tr>
<tr>
<td></td>
<td>Placebo, Diphenhydramine</td>
<td>Parallel design</td>
<td>2</td>
<td>Kay et al 1997, Kay et al 1999</td>
</tr>
<tr>
<td></td>
<td>Placebo Chlorpheniramine</td>
<td>Incomplete information</td>
<td>1</td>
<td>de Roock et al 1992</td>
</tr>
</tbody>
</table>
Table 2.2: A list of studies excluded from the review (cont.)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>OTHER TREATMENTS IN STUDY</th>
<th>REASON FOR EXCLUSION</th>
<th>NO OF STUDIES</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mizolastine</td>
<td>Placebo</td>
<td>Alcohol interaction</td>
<td>1</td>
<td>Patat et al 1994</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Placebo</td>
<td>No verum</td>
<td>1</td>
<td>Molson et al 1966</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>No placebo</td>
<td>1</td>
<td>Bagian &amp; Ward 1994</td>
</tr>
<tr>
<td></td>
<td>Clemastine</td>
<td>No placebo</td>
<td>1</td>
<td>Hindmarch &amp; Parrott 1978a</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Placebo</td>
<td>Alcohol interaction</td>
<td>1</td>
<td>Bhatti &amp; Hindmarch 1989</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>No verum</td>
<td>1</td>
<td>Murri et al 1992</td>
</tr>
<tr>
<td></td>
<td>Azatadine</td>
<td>Parallel design</td>
<td>1</td>
<td>Lunscombe et al 1983</td>
</tr>
<tr>
<td>Triprolidine</td>
<td>Brompheniramone</td>
<td>No placebo</td>
<td>1</td>
<td>Nicholson 1979</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>No placebo</td>
<td>2</td>
<td>Borland &amp; Nicholson 1984, Bye et al 1974</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>No verum</td>
<td>1</td>
<td>Bye et al 1977</td>
</tr>
</tbody>
</table>
For each drug at all doses tested, results have been listed using the categorisation of tests presented in table 2.1, according to whether there was a statistically significant finding of 'impairment' or 'no impairment'. The psychometric methods used to determine CNS adverse effects were identified as either 'objective' or 'subjective'. Using the categorisation listed in table 2.1, categories A-O were considered as objective and category P as subjective measures of performance.

It is important to make a distinction between a drug's tendency to induce subjective drowsiness and its potential to influence the objective assessment of CNS function and psychological performance (Hindmarch & Rombaut 1995). Objective tests require psychomotor performance of some sort by the subject. The performance measure is a physical one: time, number, frequency etc. Subjective tests require a subject to indicate an impression, feeling or opinion, usually on a questionnaire or a visual analogue rating scale.

Subjective tests usually form a part of a battery of tests and when combined with a objective measures, they can provide supportive data to the objective evidence for the presence or absence of CNS adverse effects. However when used in isolation, the outcome measures are unreliable in that for example, a given dose of an antihistamine may produce significant effects on a number of scales in one experiment, but no significant effects on the same scales in a second study, even with the same researchers conducting the experiments (White & Rumbold 1988).

If a statistically significant difference (p<0.05 or better) between the test drug and placebo was found on a specific psychometric test indicating an impaired CNS activity, then that test score was listed as an example of 'impairment'. This was done for each and every psychometric test in all the studies reviewed.
This sub-division of tests as objective or subjective was done because it is widely accepted that discrepancies exist between subjective reports of impairments and objective assessments of CNS function (Ahn & Barnett 1986, Mattila et al 1986, Nicholson & Stone 1986).

Based on objective evidence, the PIR for each antihistamine (PIR-O) was then calculated using the formula described in figure 2.3, which is indicative of each antihistamine’s inherent potential for disrupting cognitive and psychomotor performance. The same procedure was repeated to calculate the PIR for each antihistamine using the subjective reports of sedation (PIR-S).

The objective and subjective tests were subsequently combined and an overall PIR was calculated for each antihistamine.

Following the calculation of PIR values for all AHs, a sub-group was then selected for additional analysis. This was conducted with the currently available second generation AHs only, in order to allow a like-like comparison without the first generation AHs known to cause sedation. Using the PIR formula, the PIR-O and PIR-S together with an overall PIR value was recalculated for every second generation antihistamine to enable the ranking of these AHs (without including the first generation AHs) as regards their potential for disrupting psychomotor performance.

2.3 Results

A total of seventy-three placebo and verum controlled studies were reviewed (table 2.3). This comprised data on a total of 23 AHs, of which 14 are classed as second-generation AHs. Nine traditional first generation AHs were reviewed - they were almost always included in studies as positive internal controls.
Both acute (A) and repeated (R) dosing regimens were included. All studies used a double blind crossover design.

Table 2.4 provides a summary of the number of times impairments were detected using both objective and subjective measures with all AHs, as well as the number of times in which both objective and subjective tests failed to detect impairments with all the AHs under review.

It is evident from these studies, which are considered to be the most adequately controlled, that most of the AHs under investigation do possess some sedative properties at some point in the dose ranges investigated. However, it is the first generation AHs, which consistently impair performance at all doses tested, whereas the second-generation AHs have a generally lower sedation index, although differences exist between the individual drugs.
Table 2.3: Placebo and verum controlled studies with all AHs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>TESTS SHOWING NO IMPAIRMENT</th>
<th>TESTS SHOWING IMPAIRMENT</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Objective</td>
<td>Subj ective</td>
<td>Objective</td>
</tr>
<tr>
<td>Acrivastine</td>
<td>4mg (A)</td>
<td>B, C</td>
<td>P</td>
<td>A, B</td>
</tr>
<tr>
<td></td>
<td>8mg (A)</td>
<td>A, 3B, 2C</td>
<td>2P</td>
<td>A, B</td>
</tr>
<tr>
<td></td>
<td>16mg (A)</td>
<td>B, C</td>
<td>P</td>
<td>A, B</td>
</tr>
<tr>
<td></td>
<td>24mg (A)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10mg (R)</td>
<td>A, I, N</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20mg (A)</td>
<td>C, E, F</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30mg (A)</td>
<td>A, D</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40mg (A)</td>
<td>E</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4mg (A)</td>
<td>2B, F, K</td>
<td>2P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8mg (A)</td>
<td>2B, F, K</td>
<td>2P</td>
<td></td>
</tr>
<tr>
<td>Brompheniramine</td>
<td>12mg (R)</td>
<td>2C, D, J</td>
<td>P</td>
<td>B</td>
</tr>
<tr>
<td>DRUG</td>
<td>DOSE</td>
<td>TESTS SHOWING NO IMPAIRMENT</td>
<td>TESTS SHOWING IMPAIRMENT</td>
<td>REFERENCES</td>
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<td>-----------</td>
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<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Objective</td>
<td>Subjective</td>
<td>Objective</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>2.5mg (A)</td>
<td>B, D, O</td>
<td>P</td>
<td>C</td>
</tr>
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<td></td>
<td>15mg (A)</td>
<td>E, I</td>
<td>4P</td>
<td>C</td>
</tr>
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<td></td>
<td>20mg (A)</td>
<td>2A, 2B, 2D, 2G</td>
<td></td>
<td>C, D, N</td>
</tr>
<tr>
<td></td>
<td>20mg (R)</td>
<td>N</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4mg (R)</td>
<td>B, 2C, D, E, H, J, M</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8mg (A)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>10mg (A)</td>
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<td></td>
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</tr>
<tr>
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<td>12mg (A)</td>
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<tr>
<td></td>
<td>12mg (R)</td>
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</tr>
<tr>
<td></td>
<td>16mg (A)</td>
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</table>
Table 2.3: Placebo and *verum* controlled studies with all AHs (cont.)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>TESTS SHOWING NO IMPAIRMENT</th>
<th>TESTS SHOWING IMPAIRMENT</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Objective</td>
<td>Subjective</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1mg (R)</td>
<td>B, 2C, D, J</td>
<td>B, D, J</td>
<td>Peck et al 1975, Reinberg et al 1978</td>
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<tr>
<td></td>
<td>3mg (A)</td>
<td>B</td>
<td>B, N</td>
<td>Hopes et al 1992, Patat et al 1994</td>
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<td>Cyclizine</td>
<td>50mg (A)</td>
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<td>P</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>100mg (A)</td>
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<td>P</td>
<td>Vermeeren &amp; O’Hanlon 1998</td>
</tr>
<tr>
<td></td>
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<td>50mg (A)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50mg (R)</td>
<td>3P</td>
<td>A, 2N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C, D, 2E, F, H, I, J, M</td>
<td>16P</td>
<td></td>
</tr>
<tr>
<td>DRUG</td>
<td>DOSE</td>
<td>TESTS SHOWING NO IMPAIRMENT</td>
<td>TESTS SHOWING IMPAIRMENT</td>
<td>REFERENCES</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>Objective</td>
<td>Subjective</td>
<td>Objective</td>
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<td>Ebastine</td>
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<tr>
<td></td>
<td></td>
<td>A</td>
<td>P</td>
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<tr>
<td></td>
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<td>2B, 3C, D, E, H, N</td>
<td>3P</td>
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<tr>
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<td></td>
<td>A</td>
<td>P</td>
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<tr>
<td></td>
<td>20mg (A)</td>
<td>2B, C, D, H</td>
<td>2P</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>A</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20mg (R)</td>
<td>2B, C, D, H</td>
<td>2P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30mg (A)</td>
<td>B, D, O</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30mg (R)</td>
<td>B, D, O</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A, B, C, I</td>
<td>3P</td>
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</tr>
<tr>
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<td>120mg (A)</td>
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<td>3P</td>
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<td>3P</td>
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</tr>
<tr>
<td></td>
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<td>A, B, C, I</td>
<td>3P</td>
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<tr>
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<td>180mg (A)</td>
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<td>3P</td>
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<td></td>
<td></td>
<td>A, B, C, I</td>
<td>3P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>240mg (A)</td>
<td>2B, C, E, I, N, O</td>
<td>3P</td>
<td></td>
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<td></td>
<td></td>
<td>A, B, C, I</td>
<td>3P</td>
<td></td>
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<tr>
<td></td>
<td>240mg (R)</td>
<td>2B, C, E, I, N, O</td>
<td>3P</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A, B, C, I</td>
<td>3P</td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>20mg (A)</td>
<td>B</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20mg (R)</td>
<td>B</td>
<td>P</td>
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<tr>
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<td>B</td>
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<tr>
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<td></td>
<td>B</td>
<td>P</td>
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</tr>
<tr>
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<td>2B</td>
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<td>2B</td>
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<td>2B</td>
<td>3P</td>
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<td>Ketotifen</td>
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<td>N</td>
<td>2P</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>N</td>
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Table 2.3: Placebo and verum controlled studies with all AHs (cont.)

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<td>P</td>
<td>Roth et al 1987</td>
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<tr>
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<td>20mg (R)</td>
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<td>P</td>
<td>Bradley &amp; Nicholson 1987, Shamsi &amp; Hindmarch 1999a, Roth et al 1987</td>
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<td>B, 2E, I</td>
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<tr>
<td>Mequitazine</td>
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<td>Nicholson &amp; Stone 1983</td>
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Table 2.3: Placebo and *verum* controlled studies with all AHs (cont.)

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<td>G, O</td>
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<td>P</td>
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<td>20P</td>
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<td>P</td>
<td>Danjou et al 1990, Fink &amp; Irwin 1979, Gaillard et al 1988</td>
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Table 2.3: Placebo and *verum* controlled studies with all AHs (cont.)

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<th>TESTS SHOWING IMPAIRMENT</th>
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<td>Objective</td>
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<td>B, I</td>
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<td></td>
<td>5mg (R)</td>
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<td>A, I</td>
<td>P</td>
</tr>
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<td>7.5mg (A)</td>
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<td>D, E</td>
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<td>15mg (R)</td>
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<td>NO OF TESTS SHOWING IMPAIRMENT (I)</td>
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<td></td>
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<td>% Impairment</td>
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<td></td>
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2.3.1 First Generation AHs

The most important finding is that the traditional AHs included as positive controls behave as expected in that they consistently impair performance on a large number of tests measuring different aspects of cognitive and psychomotor performance (Clarke & Nicholson 1978, Gaillard et al 1988, Goetz et al 1991, Hindmarch et al 1999, Hopes et al 1992, Shamsi & Hindmarch 1999a, Shamsi & Hindmarch 1999b, Vermeeren & O’Hanlon 1998, Witek et al 1995). This impairment is evident on both objective and subjective measures. Of the 381 tests used to investigate the effects of traditional AHs, 278 (73%) successfully detected impairments and 103 tests (27%) were unable to demonstrate significant deterioration of cognitive and psychomotor abilities. In contrast, 587 tests were used in investigating the CNS adverse effects of the second generation AHs, of which only 72 tests were indicative of impairments (12%).

Chlorpheniramine (4-16mg), diphenhydramine (25-150mg), hydroxyzine (20-50mg) promethazine (10-30mg) and triprolidine (1.25-15mg) were exclusively used as verum, whereas brompheniramine (12mg), clemastine (1-4mg), ketotifen (1-2mg) and oxatomide (30mg) were included in a number of studies as a comparator rather than a positive control.

The administration of triprolidine in a range of doses, resulted in widespread impairment of various aspects of cognitive and psychomotor performance (Brookhuis et al 1993, Cohen et al 1987, Riedel et al 1990b, Rombaut et al 1991, Shamsi & Hindmarch 1999b, Volkerts et al 1992). There were however, a number of studies in which few or no impairments were reported but these occurred mainly when lower range of doses were administered (Cohen et al 1985, Hamilton et al 1982, Peck et al 1975). A number of other factors could have contributed to these findings. Firstly there is the use of the ‘slow release’ formulation of the substance, which affects both the clinical activity and
psychometric consequences of taking the drug across a longer time scale (Shamsi & Hindmarch 1999b). As a result of the administration of a slow release formulation, the acute dose peak of sedative activity is 'smoothed out' over a longer time period, which may well be outside the time frame of psychometric testing in the particular study. The times of psychometric testing were not necessarily consistent or identical across the various studies, which together with different pharmacodynamics brought about by various formulations, could have resulted in an increase in the variability of the observed effects. In addition, a substantial inter-individual variability exists with regard to antihistamine-induced sedation.

As the first generation of AHs are highly lipophilic (Simons 1995, Woodward 1988) and cross the blood brain barrier (Passalacqua et al 1996, Simons & Simons 1991), impairments frequently occur following the administration of these compounds.

However, the lack of any objective evidence of impairment with the lower doses of loratadine (Betts et al 1988, Bradley & Nicholson 1987, Hindmarch et al 1999, Roth et al 1987) and cetirizine (Gengo & Gabos 1987, Gengo et al 1990, Shamsi & Hindmarch 1999a, Simons et al 1995), for example, may be due to the fact that the concentrations achieved in the CNS are below those required to cause detrimental effects on cognitive and psychomotor abilities or that the lower threshold of sensitivity of the psychometric test itself has not been reached (Woodworth & Schlosberg 1958). Inter-study variability in dose regimens and testing programmes may also account for the difficulty in detecting impairment in a number of instances.

Tables 2.5 and 2.6 list the PIR values calculated for all the AHs included in the literature review based on objective and subjective tests used respectively. It is evident that all first generation AHs have a PIR value close to 2, whereas the second-generation AHs have a lower ratio with the majority resting under 1, regardless of whether impairments
are detected using objective tests or subjective measures. However, there are differences in the ranking order of these AHs and the statistical significance of the PIR, depending on whether objective or subjective tests are used in the calculation of the impairment ratio.

As discussed previously, subjective assessments of sedation are not as reliable as objective measures of performance, because by their very nature, sleepiness, somnolence and sedation can impair the self assessment of awareness and thus result in misleading results (Hindmarch & Shamsi 1999). In addition, they are much more likely to be influenced by transient fluctuations of attention and other factors such as the cognitive demand characteristics of the task and the environment than are objective measures of performance (Walsh et al 1992). Therefore conclusions about the sedative potential of an antihistamine can not be made solely on data from subjective tests.

In light of the above, it is therefore evident that greater confidence can be placed on the PIR values calculated using objective measures of performance. Using these PIR-O values, the AHs are ranked as regards their potential to cause impairment of cognitive and psychomotor performance (table 2.5).

Promethazine possesses the highest PIR ratio with a value of 3.09, followed by hydroxyzine (2.25), triprolidine (2.21), clemastine (2.21), diphenhydramine (2.03) and chlorpheniramine (1.88). In addition, the calculated PIR values for the first generation AHs are all statistically significant (p<0.01) and thus can be confidently included in the ranking table.
Using the data from table 2.6, the ranking order is changed although the PIR value for all first generation AHs still lies close to 2. Hydroxyzine has the highest PIR value of 2.57, followed by triprolidine (2.29), diphenhydramine (2.26), promethazine (2.24), clemastine (1.80) and chlorpheniramine (1.74).

Despite these differences in the ranking order of the first generation AHs, depending on whether the PIR calculation is based on objective or subjective tests, it can be concluded that the first generation AHs are inherently sedative and cause significant impairment of cognitive and psychomotor function. Furthermore, the high and statistically significant PIR values obtained with these AHs provides support for the use of this method in predicting the sedative effects of AHs.
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<th>Drug</th>
<th>a</th>
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<th>c</th>
<th>d</th>
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<th>$X^2$ with 1 d.f</th>
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<td>436</td>
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<td>440</td>
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<td>243</td>
<td>444</td>
<td>0.00</td>
<td>10.23**</td>
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<td>243</td>
<td>456</td>
<td>0.00</td>
<td>3.86*</td>
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<td>243</td>
<td>460</td>
<td>0.00</td>
<td>1.81 (NS)</td>
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<td>0.11 (NS)</td>
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<td>13.87***</td>
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<td>0.23 (NS)</td>
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<td>0</td>
<td>240</td>
<td>466</td>
<td>2.94</td>
<td>3.22 (NS)</td>
</tr>
<tr>
<td>Promethazine</td>
<td>31</td>
<td>1</td>
<td>212</td>
<td>465</td>
<td>3.09</td>
<td>55.43***</td>
</tr>
</tbody>
</table>

- **a**: Number of tests showing 'impairment' with a named antihistamine;
- **b**: Number of tests showing 'no impairment' with the named antihistamine;
- **c**: Number of tests showing 'impairment' with all other antihistamines in the database;
- **d**: Number of tests which show 'no impairment' with all other AHs in the database.

NS = Not Significant

* = Significant at 5% level when $X^2$ is equal to or greater than 3.84

** = Significant at 1% level when $X^2$ is equal to or greater than 6.64

*** = Significant at the 0.1% when $X^2$ is equal to or greater than 10.83
<table>
<thead>
<tr>
<th>Drug</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>PIR</th>
<th>$X^2$ with 1 d.f</th>
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<td>148</td>
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<td>1.39 (NS)</td>
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<td>0.22 (NS)</td>
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<td>6.44*</td>
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<td>123</td>
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<td>5.99*</td>
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<tr>
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<td>0.27 (NS)</td>
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<tr>
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<td>151</td>
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<td>0.22 (NS)</td>
</tr>
<tr>
<td>Cyclizine</td>
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<td>151</td>
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<td>0.22 (NS)</td>
</tr>
<tr>
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<td>98</td>
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<td>1.74</td>
<td>3.27 (NS)</td>
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<tr>
<td>Clemastine</td>
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<td>1.80</td>
<td>4.30*</td>
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<tr>
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<td>151</td>
<td>2.24</td>
<td>6.79**</td>
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<tr>
<td>Diphenhydramine</td>
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<td>84</td>
<td>147</td>
<td>2.26</td>
<td>19.74***</td>
</tr>
<tr>
<td>Triprolidine</td>
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<td>86</td>
<td>148</td>
<td>2.29</td>
<td>18.99***</td>
</tr>
<tr>
<td>Temelastine</td>
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<td>0</td>
<td>106</td>
<td>152</td>
<td>2.43</td>
<td>0.03 (NS)</td>
</tr>
<tr>
<td>Ketotifen</td>
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<td>0</td>
<td>104</td>
<td>152</td>
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<td>2.21 (NS)</td>
</tr>
<tr>
<td>Oxatomide</td>
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<td>104</td>
<td>152</td>
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<td>2.21 (NS)</td>
</tr>
<tr>
<td>Hydroxyzine</td>
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<td>0</td>
<td>97</td>
<td>152</td>
<td>2.57</td>
<td>12.37***</td>
</tr>
</tbody>
</table>

a: Number of tests showing 'impairment' with a named antihistamine;
b: Number of tests showing 'no impairment' with the named antihistamine;
c: Number of tests showing 'impairment' with all other antihistamines in the database;
d: Number of tests which show 'no impairment' with all other AHs in the database.

NS = Not Significant

* = Significant at 5% level when $X^2$ is equal to or greater than 3.84

** = Significant at 1% level when $X^2$ is equal to or greater than 6.64

*** = Significant at the 0.1% when $X^2$ is equal to or greater than 10.83
2.3.2 Second Generation AHs

The second generation AHs have much lower PIR values when compared to their predecessors, although the PIR for a number of these compounds is greater than zero and suggestive of a degree of sedative potential (tables 2.5 & 2.6). A closer look at table 2.3 demonstrates that the lower doses of these second-generation AHs are almost free of CNS effects but impairments become evident when higher doses are administered (Gaillard et al 1988, Nicholson & Turner 1998, Riedel et al 1990, Shamsi & Hindmarch 1999b, Vuurman et al 1994). This suggests that some passage through the blood brain barrier occurs with these AHs and at the lower dose range, concentrations in the CNS are not sufficient to cause impairments. Increasing the dose results in sufficient concentration of the drug in the CNS, which consequently manifests as an impairment of particular tests. Some of the second-generation AHs are claimed to be non-sedating (Kay & Harris 1999, Kay et al 1999, Roberts & Gispert 1999, Rosenzweig & Patat 1999) due to their inability to cross the blood brain barrier. However if no penetration to the CNS occurs, then they must be free of sedation regardless of the doses administered and thus show no significant impairments on any of the tests of cognitive and psychomotor function. These AHs with which there is evidence of impairment at higher doses, should therefore not be referred to as non-sedating as this does not take into the account the impairments which occur with the administration of higher doses. It would be better to regard them as possessing a ‘window’ of non-impairment, but this in itself is of no interest in isolation from considerations of the clinical efficacy/potency of a particular dose level, which is outside the scope of this thesis.

Results from tables 2.3 & 2.4 demonstrate that impairments were evident with several of the second generation AHs across a range of doses. Mizolastine was investigated in a total of 4 studies utilising 62 objective tests, of which 16 demonstrated impairments.
Subjective reports were utilised in 12 instances of which 9 were associated with impairments. In all cases, detrimental effects were demonstrated following the administration of higher doses. It is therefore clear that at its recommended dose of 10mg, mizolastine is free of adverse CNS effects and significant impairments become evident only after the administration of higher doses.

Terfenadine was investigated in 32 studies across a range of doses. Of the 117 objective tests investigating its CNS profile, there were 7 instances in which detrimental effects were demonstrated. The use of terfenadine resulted in subjective reports of sedation only in 2 instances from a total of 37 times that this measure was used. Given the large number of tests, which have failed to detect psychomotor impairments with this antihistamine, the few reports of impairments are more likely to be due to chance than any other factor. Cetirizine was investigated in 15 studies, utilising a total of 93 tests, of which 14 demonstrated detrimental CNS effects across a range of doses. Of the 56 objective tests used in investigating the CNS profile of cetirizine, 6 were associated with significant impairments. These impairments were mostly evident following the administration of higher doses of cetirizine. There was one report of impairment on a tracking task following a 5mg dose of cetirizine and there was a single report of impairment on the multiple sleep latency task (MSLT) following the administration of 10mg cetirizine. This therefore indicates that with cetirizine, some penetration of the CNS occurs resulting in a measurable impairment, although the observed impairments at the lower doses may be due to a number of other factors such as inter-individual variability and chance.

The number of well designed and appropriately controlled studies with loratadine were surprisingly low, considering its position in the antihistamine market. Loratadine was investigated in 9 studies, which fulfilled the criteria for inclusion in the review. Of the
62 tests used, 11 were indicative of impairments across a range of doses. A total of 47 objective tests were utilised in assessing the CNS profile of loratadine, of which 10 were indicative of significant impairments, although the impairments became evident following the administration of higher doses (20-40mg). The high incidence of impairments with loratadine resulted in a PIR-O value of 0.60, which failed to reach statistical significance (table 2.5). In other words, in comparing the CNS effects of loratadine with all other AHs, it was not possible to differentiate loratadine from all other AHs including the first generation AHs, which are known to cause impairment of cognitive and psychomotor function. Such findings make for difficulties in classifying loratadine as a non-sedating antihistamine (Kay et al 1997, Kay et al 1999) and emphasise the need for labelling loratadine as having a window of “no sedation” at 10mg.

Although Kay & Harris (1999) have concluded that findings with a 10mg dose of loratadine obviate the need for assessing the CNS effects of loratadine at the higher dose, the findings from this review suggest the contrary. Loratadine has been shown to cause impairments at the higher doses in a number of well designed studies (Gaillard et al 1988, Riedel et al 1990, Shamsi & Hindmarch 1999a) and the PIR value of 0.60 with a non-significant $X^2$ statistic further support the claim (Howarth 1998) that loratadine should be classified as a 2b category antihistamine in which CNS adverse effects become evident when higher doses are administered.

In contrast to the objective evidence, there was only one incidence in which subjective sedation was reported following the administration of loratadine (Riedel et al 1990b). As a result, a low PIR value (0.15, $p<0.05$) was obtained when the subjective evidence was taken into consideration. However for reasons discussed before, results obtained with subjective assessments must be treated with caution and conclusions about the sedative potential of an antihistamine must not be based solely on data obtained from subjective
measures (Hindmarch & Shamsi 1999).

Although the use of cetirizine is also associated with cognitive and psychomotor impairments when higher doses are administered, it is important to highlight one important difference between these two compounds.

Cetirizine is an extremely potent antihistamine as demonstrated by its ability to inhibit the histamine induced weal and flare reaction (Grant et al 1999, Rihoux et al 1990, Simon et al 1990, Urien et al 1999). Relief of allergy symptoms is readily achieved with the lower doses of cetirizine (Day et al 1997, Meltzer et al 1996, Rihoux et al 1998) and higher doses are only rarely required in certain patient populations. In terms of potency, as measured by the histamine induced weal and flare test, 40mg loratadine is required to achieve a similar inhibition of the weal and flare response to cetirizine 10mg (Rihoux et al 1990).

Whereas the 10mg dose of cetirizine is free from measurable effects on cognitive and psychomotor performance, a 40mg dose of loratadine produces significant residual CNS adverse effects (Gaillard et al 1988, Riedel et al 1990b, Shamsi & Hindmarch 1999a). The findings from this literature review therefore, do not support the claim that the second-generation AHs are completely non-sedating. However, it is evident that a ‘dose window’ exists for a number of these AHs, within which these AHs are free of detrimental effects on measures of cognitive and psychomotor performance. It is only when these doses are exceeded, that impairments become evident.

Based on objective evidence, five of the fourteen second generation AHs achieved a PIR value of zero (table 2.5). These were fexofenadine, a metabolite of terfenadine, ebastine, astemizole, levocabastine and temelastine.

The PIR value obtained with temelastine does not warrant further discussion as it failed to reach statistical significance. In addition, temelastine was an investigational
compound, which was studied in one clinical study and is not available in the antihistamine market. The findings with levocabastine must be treated with caution as only one controlled study employing 10 objective tests has investigated the sedative effects of this antihistamine and thus PIR value of zero is derived only from the results of one study (Rombaut et al 1991). In line with the PIR calculated from the objective evidence, the PIR based on subjective reports was also zero, although only two subjective assessments were used in deriving this value. Further research is therefore required before levocabastine can be confidently placed in the non-sedating category.

In contrast to levocabastine, astemizole was studied in 9 studies employing twenty-two objective tests in which no impairments were detected at any of the doses tested. The derived PIR based on subjective evidence was supportive of the above, with no evidence of self-reported sedation in 10 out of 10 instances used. However reports of adverse cardiovascular effects (DuBuske 1999, Woosley 1996) following overdose with astemizole has led to the drug being withdrawn.

In assessing the CNS effects of ebastine, 26 objective tests failed to demonstrate impairments of performance, thus resulting in a PIR value of 0.00. However there were two subjective reports of sedation following the administration of a 30mg dose in one study (Shamsi & Hindmarch 1999b). Although subjective reports can be unreliable and judgements regarding the CNS profile of a drug cannot be based solely on subjective measures, these findings cannot be ignored. If an antihistamine is to be identified as ‘non-sedating’ at all doses administered, the derived PIR value using both subjective and objective evidence must be zero and furthermore the calculated PIR value must be of statistical significance. As ebastine has only been studied in a small number of controlled studies, further research is required to establish its CNS profile and allow its
ranking amongst those which can claim to be ‘non-sedating’ regardless of the dose administered.

The only remaining antihistamine with a PIR value of zero is fexofenadine.

Fexofenadine, which is the active metabolite of terfenadine, is a recent addition to the list of non-sedating AHs. To date, three placebo with verum controlled studies employing 39 tests have investigated the effects of various doses up to 240mg (Hindmarch et al 1999, Stone et al 1999, Vermeeren & O’Hanlon 1998). Within these doses, fexofenadine lacked any objectively determined sedative activity and did not impair cognitive and psychomotor performance. Supportive to the objective evidence, subjective tests were used in 9 instances and in all cases, there were no reports of sedation when tested across a range of doses. The clinical dosage regimen for fexofenadine in the treatment of SAR is 120mg and 180mg for the treatment of chronic idiopathic urticaria (CIU). Trials with this drug have however investigated its effects up to 240mg (Stone et al 1999). This dose is in excess of the clinical dose and no impairments are evident on any of the tests, which might support Howarth’s (1998) notion that fexofenadine may need to be classified as a 2c or even a third generation antihistamine at least for its lack of CNS activity.

According to the classification proposed by Howarth (1998), cetirizine and loratadine are classified as category 2b AHs, implying that some sedation may occur when higher doses are administered. Terfenadine and astemizole may be associated with cardiotoxic effects and are thus classified as class 2a AHs.

Although it may be argued that the number of studies conducted with fexofenadine were small to allow a comparison with other second generation AHs, it is worthy of note that only nine studies with loratadine were of satisfactory design to be included in the review. Cetirizine was investigated in 15 well designed studies, utilising a wide range of tests and therefore greater confidence can be placed in ranking cetirizine as free of detrimental
effects when administered within its established ‘dose window’ of 10mg. The confidence in cetirizine’s position is further reinforced with the highly significant $X^2$ statistic.

Increasing the cell frequencies in the formula outlined in figure 2.2 increases the accuracy of the calculated PIR. Therefore, following the calculation of the PIR-O and PIR-S all AHs (tables 2.5 & 2.6), the objective and subjective tests were combined to calculate an overall PIR value for each antihistamine (table 2.7). It is evident that despite combining the objective and subjective tests, the ranking order of the second-generation AHs is not generally affected, although the PIR values are slightly altered. Fexofenadine with a PIR value of zero is ranked at the top followed by astemizole (0.00), levocabastine (0.00), terfenadine (0.14), ebastine (0.14), cetirizine (0.33), loratadine (0.48) and mizolastine (0.70). Similarly, the combination of the objective and subjective tests has changed the rank order of the first generation AHs, although the values are still close to 2 and of statistical significance. This supports the previous findings and confirms the ability of these compounds to cause significant impairment of cognitive and psychomotor function.
Table 2.7: Calculation of an overall PIR for all AHs included in the review

<table>
<thead>
<tr>
<th>Drug</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>PIR</th>
<th>$X^2$ with 1 d.f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine</td>
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<td>350</td>
<td>579</td>
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<tr>
<td>Terfenadine</td>
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<td>341</td>
<td>473</td>
<td>0.14</td>
<td>71.35***</td>
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<td>79</td>
<td>336</td>
<td>539</td>
<td>0.39</td>
<td>18.85***</td>
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<tr>
<td>Tazifylline</td>
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<td>18</td>
<td>347</td>
<td>600</td>
<td>0.39</td>
<td>3.53 (NS)</td>
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<tr>
<td>Temelastine</td>
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<td>349</td>
<td>612</td>
<td>0.39</td>
<td>0.66 (NS)</td>
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<tr>
<td>Loratadine</td>
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<td>567</td>
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<td>8.90**</td>
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<td>346</td>
<td>604</td>
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<td>0.99 (NS)</td>
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<tr>
<td>Azatadine</td>
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<td>14</td>
<td>346</td>
<td>604</td>
<td>0.61</td>
<td>0.99 (NS)</td>
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<tr>
<td>Mequitazine</td>
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<td>609</td>
<td>0.69</td>
<td>0.26 (NS)</td>
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<tr>
<td>Cyclizine</td>
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<td>6</td>
<td>348</td>
<td>612</td>
<td>0.69</td>
<td>0.08 (NS)</td>
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<tr>
<td>Brompheniramine</td>
<td>2</td>
<td>5</td>
<td>348</td>
<td>613</td>
<td>0.79</td>
<td>0.00 (NS)</td>
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<tr>
<td>Chlorpheniramine</td>
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<td>15</td>
<td>323</td>
<td>603</td>
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<td>13.80***</td>
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<tr>
<td>Clemastine</td>
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<td>17</td>
<td>309</td>
<td>601</td>
<td>2.08</td>
<td>30.30***</td>
</tr>
<tr>
<td>Ketotifen</td>
<td>3</td>
<td>1</td>
<td>347</td>
<td>617</td>
<td>2.08</td>
<td>1.21 (NS)</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>66</td>
<td>30</td>
<td>284</td>
<td>588</td>
<td>2.11</td>
<td>47.49***</td>
</tr>
<tr>
<td>Triprolidine</td>
<td>72</td>
<td>29</td>
<td>278</td>
<td>589</td>
<td>2.22</td>
<td>58.60***</td>
</tr>
<tr>
<td>Hydroxyzine</td>
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<td>4</td>
<td>328</td>
<td>614</td>
<td>2.43</td>
<td>25.06***</td>
</tr>
<tr>
<td>Oxatomide</td>
<td>6</td>
<td>0</td>
<td>344</td>
<td>618</td>
<td>2.80</td>
<td>8.06**</td>
</tr>
<tr>
<td>Promethazine</td>
<td>39</td>
<td>2</td>
<td>311</td>
<td>616</td>
<td>2.84</td>
<td>61.85***</td>
</tr>
</tbody>
</table>

a: Number of tests showing 'impairment' with a named antihistamine;
b: Number of tests showing 'no impairment' with the named antihistamine;
c: Number of tests showing 'impairment' with all other antihistamines in the database;
d: Number of tests which show 'no impairment' with all other AHs in the database.

NS = Not Significant

* = Significant at 5% level when $X^2$ is equal to or greater than 3.84

** = Significant at 1% level when $X^2$ is equal to or greater than 6.64

*** = Significant at the 0.1% when $X^2$ is equal to or greater than 10.83
2.3.3 Currently Available First & Second Generation AHs

Of the 23 AHs reviewed in this chapter, only 11 are currently available either as OTC preparations or as prescription only medicines in the United Kingdom. In order to clarify the findings with the currently available AHs, tables 2.8, 2.9 & 2.10 list the PIR values together with the calculated $X^2$ statistic for each of these AHs.

Table 2.8: Rank order of currently available AHs as determined by the PIRs based on objective measures

<table>
<thead>
<tr>
<th>Drug</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>PIR</th>
<th>$X^2$ with 1 d.f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine</td>
<td>0</td>
<td>30</td>
<td>243</td>
<td>436</td>
<td>0.00</td>
<td>14.78***</td>
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<td>10</td>
<td>243</td>
<td>444</td>
<td>0.00</td>
<td>3.86*</td>
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<td>Terfenadine</td>
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<td>110</td>
<td>236</td>
<td>356</td>
<td>0.15</td>
<td>48.29***</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>6</td>
<td>50</td>
<td>237</td>
<td>416</td>
<td>0.30</td>
<td>13.87***</td>
</tr>
<tr>
<td>Loratadine</td>
<td>10</td>
<td>37</td>
<td>233</td>
<td>429</td>
<td>0.60</td>
<td>3.18 (NS)</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>18</td>
<td>11</td>
<td>225</td>
<td>455</td>
<td>1.88</td>
<td>9.12**</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>43</td>
<td>25</td>
<td>200</td>
<td>441</td>
<td>2.03</td>
<td>26.60***</td>
</tr>
<tr>
<td>Triprolidine</td>
<td>51</td>
<td>25</td>
<td>192</td>
<td>441</td>
<td>2.21</td>
<td>39.12***</td>
</tr>
<tr>
<td>Clemastine</td>
<td>31</td>
<td>13</td>
<td>212</td>
<td>453</td>
<td>2.21</td>
<td>25.58***</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>12</td>
<td>4</td>
<td>231</td>
<td>462</td>
<td>2.25</td>
<td>10.27**</td>
</tr>
<tr>
<td>Promethazine</td>
<td>31</td>
<td>1</td>
<td>212</td>
<td>465</td>
<td>3.09</td>
<td>55.43***</td>
</tr>
</tbody>
</table>

a: Number of tests which showed ‘impairment’ with the named antihistamine;
b: Number of tests which showed ‘no impairment’ with the named antihistamine;
c: Number of tests which showed ‘impairment’ with all other AHs in the database;
d: Number of tests which showed ‘no impairment’ with all other AHs in the database;
NS= Not significant compared to all other AHs in the database;
* = Significant at 5 % level when $X^2$ is equal to or greater than 3.84
** = Significant at 1% level when $X^2$ is equal to or greater than 6.64
*** = Significant at the 0.1% when $X^2$ is equal to or greater than 10.83
Table 2.9: Rank order of currently available AHs as determined by the PIRs based on subjective measures

<table>
<thead>
<tr>
<th>Drug</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>PIR</th>
<th>$X^2$ with 1 d.f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine</td>
<td>0</td>
<td>9</td>
<td>107</td>
<td>143</td>
<td>0.00</td>
<td>4.92*</td>
</tr>
<tr>
<td>Levocabastine</td>
<td>0</td>
<td>2</td>
<td>107</td>
<td>150</td>
<td>0.00</td>
<td>0.22 (NS)</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>2</td>
<td>35</td>
<td>105</td>
<td>117</td>
<td>0.11</td>
<td>21.26***</td>
</tr>
<tr>
<td>Loratadine</td>
<td>1</td>
<td>14</td>
<td>106</td>
<td>138</td>
<td>0.15</td>
<td>6.44*</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>8</td>
<td>29</td>
<td>99</td>
<td>123</td>
<td>0.48</td>
<td>5.99*</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>9</td>
<td>4</td>
<td>98</td>
<td>148</td>
<td>1.74</td>
<td>3.27 (NS)</td>
</tr>
<tr>
<td>Clemastine</td>
<td>10</td>
<td>4</td>
<td>97</td>
<td>148</td>
<td>1.80</td>
<td>4.30*</td>
</tr>
<tr>
<td>Promethazine</td>
<td>8</td>
<td>1</td>
<td>99</td>
<td>151</td>
<td>2.24</td>
<td>6.79**</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>23</td>
<td>5</td>
<td>84</td>
<td>147</td>
<td>2.26</td>
<td>19.74***</td>
</tr>
<tr>
<td>Triprolidine</td>
<td>21</td>
<td>4</td>
<td>86</td>
<td>148</td>
<td>2.29</td>
<td>18.99***</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>10</td>
<td>0</td>
<td>97</td>
<td>152</td>
<td>2.57</td>
<td>12.37***</td>
</tr>
</tbody>
</table>

a: Number of tests which showed 'impairment' with the named antihistamine;
b: Number of tests which showed 'no impairment' with the named antihistamine;
c: Number of tests which showed 'impairment' with all other AHs in the database;
d: Number of tests which showed 'no impairment' with all other AHs in the database;
NS= Not significant compared to all other AHs in the database;
* = Significant at 5 % level when $X^2$ is equal to or greater than 3.84
** = Significant at 1% level when $X^2$ is equal to or greater than 6.64
*** = Significant at the 0.1% when $X^2$ is equal to or greater than 10.83
Table 2.10: Rank order of currently available AHs as determined by the PIRs based on both objective & subjective measures

<table>
<thead>
<tr>
<th>Drug</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>PIR</th>
<th>$X^2$ with 1 d.f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine</td>
<td>0</td>
<td>39</td>
<td>350</td>
<td>579</td>
<td>0.00</td>
<td>21.41***</td>
</tr>
<tr>
<td>Levocabastine</td>
<td>0</td>
<td>12</td>
<td>350</td>
<td>606</td>
<td>0.00</td>
<td>5.39*</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>9</td>
<td>145</td>
<td>341</td>
<td>473</td>
<td>0.14</td>
<td>71.35***</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>14</td>
<td>79</td>
<td>336</td>
<td>539</td>
<td>0.39</td>
<td>18.85***</td>
</tr>
<tr>
<td>Loratadine</td>
<td>11</td>
<td>51</td>
<td>339</td>
<td>567</td>
<td>0.47</td>
<td>8.90**</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>27</td>
<td>15</td>
<td>323</td>
<td>603</td>
<td>1.84</td>
<td>13.80***</td>
</tr>
<tr>
<td>Clemastine</td>
<td>41</td>
<td>17</td>
<td>309</td>
<td>601</td>
<td>2.08</td>
<td>30.30***</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>66</td>
<td>30</td>
<td>284</td>
<td>588</td>
<td>2.11</td>
<td>47.49***</td>
</tr>
<tr>
<td>Triprolidine</td>
<td>72</td>
<td>29</td>
<td>278</td>
<td>589</td>
<td>2.22</td>
<td>58.60***</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>22</td>
<td>4</td>
<td>328</td>
<td>614</td>
<td>2.43</td>
<td>25.06***</td>
</tr>
<tr>
<td>Promethazine</td>
<td>39</td>
<td>2</td>
<td>311</td>
<td>616</td>
<td>2.84</td>
<td>61.85***</td>
</tr>
</tbody>
</table>

a: Number of tests which showed no 'impairment' with the named antihistamine;
b: Number of tests which showed 'no impairment' with the named antihistamine;
c: Number of tests which showed 'impairment' with all other AHs in the database;
d: Number of tests which showed 'no impairment' with all other AHs in the database;
NS = Not significant compared to all other AHs in the database;
* = Significant at 5% level when $X^2$ is equal to or greater than 3.84
** = Significant at 1% level when $X^2$ is equal to or greater than 6.64
*** = Significant at the 0.1% when $X^2$ is equal to or greater than 10.83

In the clinical context where considerations of potency/efficacy are of equal importance to the drug's CNS profile of possible impairment, it still has to be remembered that the CNS impairments are intrinsic to the pharmacology of the particular drug, but these summary tables do have utility in determining those drugs which are more suitable for ambulant patients.
2.3.4 PIR Re-analysis with the Second Generation AHs

In order to draw a direct like-with-like comparison between the second-generation AHs only, the PIR values were recalculated for these AHs using the same formula described in figure 2.3.

Using the data obtained from both the objective and subjective tests, an overall PIR value was calculated for each second-generation antihistamine (table 2.11). An individual analysis using only the objective or only the subjective tests was not done as the breakdown of the tests would significantly reduce the cell size and compromise the accuracy of the analysis. Furthermore, previous breakdown of the tests as either ‘objective’ or ‘subjective’ revealed that there were no significant differences in the ranking order of the AHs as regards their potential to cause cognitive and psychomotor impairments.

Using only the data with studies of second-generation AHs, it is clear that the overall ranking is not affected, although higher PIRs are obtained in the second sub-group analysis (table 2.11). This is explained by a smaller amount of data being entered for the ‘all other AHs in the database’ category. It is interesting to note that only three AHs achieved statistical significance when compared to the rest of the second generation AHs. The statistical significance of the $X^2$ indicates a difference between that specific antihistamine and the rest of the AHs included in the calculation of the PIR values.

Although indicative of a difference, the $X^2$ however, does not differentiate the direction of the change. Within the context of this review, the $X^2$ does not indicate whether the use of a specific antihistamine causes significant impairments when compared to the other AHs or whether it is devoid of detrimental effects in comparison to the other AHs.
Table 2.11: Re-calculation of PIRs for the second generation AHs using data from both objective and subjective tests:

<table>
<thead>
<tr>
<th>Drug</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>PIR</th>
<th>$X^2$ with 1 d.f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine</td>
<td>0</td>
<td>39</td>
<td>59</td>
<td>423</td>
<td>0.00</td>
<td>4.23*</td>
</tr>
<tr>
<td>Astemizole</td>
<td>0</td>
<td>32</td>
<td>59</td>
<td>430</td>
<td>0.00</td>
<td>3.24 (NS)</td>
</tr>
<tr>
<td>Levocabastine</td>
<td>0</td>
<td>12</td>
<td>59</td>
<td>450</td>
<td>0.00</td>
<td>0.63 (NS)</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>9</td>
<td>145</td>
<td>50</td>
<td>317</td>
<td>0.43</td>
<td>5.79*</td>
</tr>
<tr>
<td>Ebastine</td>
<td>2</td>
<td>35</td>
<td>57</td>
<td>427</td>
<td>0.46</td>
<td>0.83 (NS)</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>14</td>
<td>79</td>
<td>45</td>
<td>383</td>
<td>1.43</td>
<td>1.15 (NS)</td>
</tr>
<tr>
<td>Loratadine</td>
<td>11</td>
<td>51</td>
<td>48</td>
<td>411</td>
<td>1.70</td>
<td>2.21 (NS)</td>
</tr>
<tr>
<td>Acrivastine</td>
<td>4</td>
<td>14</td>
<td>55</td>
<td>448</td>
<td>2.03</td>
<td>1.22 (NS)</td>
</tr>
<tr>
<td>Mizolastine</td>
<td>19</td>
<td>55</td>
<td>40</td>
<td>317</td>
<td>2.87</td>
<td>16.06*</td>
</tr>
</tbody>
</table>

a: Number of tests which showed 'impairment' with the named antihistamine;
b: Number of tests which showed 'no impairment' with the named antihistamine;
c: Number of tests which showed 'impairment' with all other AHs in the database;
d: Number of tests which showed 'no impairment' with all other AHs in the database;

* = Significant at 5% level when $X^2$ is equal to or greater than 3.84

Examination of the data in Table 2.11 indicates that the use of mizolastine resulted in a number of impairments and the statistically significant $X^2$ indicates that these detrimental CNS effects are significantly different when compared to the other second generation AHs. However the situation is reversed with terfenadine and fexofenadine and the significant $X^2$ statistic confirms that these AHs are free from CNS impairing effects to a greater degree than the other AHs included in the analysis. The data indicates that there were 9 reports of impairments (7 objective, 2 subjective) out of the 154 tests used to investigate the CNS profile of terfenadine. Similarly with fexofenadine, there were no reports of either objectively determined or subjectively reported impairments from 39
tests across a range of doses. Comparison of the CNS effects of fexofenadine with all other AHs including the first generation AHs known to cause impairments differentiated this compound from the others indicating its non-sedative CNS profile. Furthermore, a comparison of these effects with only the second generation AHs, which are claimed to be non-sedating, once again differentiated fexofenadine as the only antihistamine with a PIR value of 0.00 which achieved statistical significance. Considering that the re-analysis was conducted with a group of AHs, which are claimed to be free of CNS effects, it was expected that no significant differences would be evident between these compounds. The fact that fexofenadine is shown to be significantly different to the other second generation AHs confirms that fexofenadine does not belong to this second generation category, thus leading further support to the classification of this fexofenadine as a 'third generation' antihistamine, at least as regards its unique profile of lack of CNS effects.
2.4 Psychometrics Sensitive to the Effects of AHs

The secondary objective of this review was to identify the tests, which are most sensitive to the central effects of AHs, i.e. to identify a psychometric test battery, which could be used with maximal effectiveness when investigating the CNS profiles of this class of compounds.

A closer look at table 2.3 clearly shows that there is a wide range of tests and techniques which are used in experimental studies of the effects of AHs on CNS variables.

2.4.1 Sensitivity of psychometrics

The sensitivity of a test can be derived by looking at the number of times a particular test successfully detects impairment in those AHs, which have been shown to cause sedation (i.e. the first generation AHs).

Although the sedative activity of all first generation AHs is well established, not all studies have used the same tests. Therefore in order to be able to make conclusions about the sensitivity of psychometric tests, the findings with all first generation AHs used in the review were pooled together. In cases where a test measured more than one aspect of information processing, it was grouped under the most relevant feature. The sensitivity of a test or a group of similar tests i.e. the ability of a test to discriminate sedation with respect to placebo was calculated by dividing the number of times impairments were detected with a specific test/test group, by the total number of times that specific test group was used (table 2.12). In order, as before, to put the sensitivity of a particular test/test group within the context of all other psychometrics, a proportional impairment detection ratio (PIDR) was calculated for each group of tests using the previously outlined formula (figure 2.2).
Table 2.12: Percentage detection rate of impairment with 1st generation AHs used as positive internal controls in all studies

<table>
<thead>
<tr>
<th>Code</th>
<th>Description of Test</th>
<th>No of times impairment detected</th>
<th>Total no of times used</th>
<th>% Detection of impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Psychomotor Performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Actual Car Driving</td>
<td>14</td>
<td>14</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>Simulated Car Driving</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Psychomotor Speed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Choice Reaction Time</td>
<td>45</td>
<td>52</td>
<td>86.5</td>
</tr>
<tr>
<td></td>
<td>Simple Reaction Time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Sensorimotor Coordination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adaptive Tracking, Critical Tracking, Continuous Tracking, Pursuit Rotor, Simulated Car Tracking, Visuo-Motor Coordination</td>
<td>28</td>
<td>36</td>
<td>77.8</td>
</tr>
<tr>
<td>D</td>
<td>CNS Arousal &amp; Information Processing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Critical Flicker Fusion</td>
<td>17</td>
<td>27</td>
<td>63.0</td>
</tr>
<tr>
<td>E</td>
<td>Digit Symbol Substitution Task, Letter Cancellation, Visual Search Task</td>
<td>25</td>
<td>44</td>
<td>56.8</td>
</tr>
<tr>
<td>F</td>
<td>Grammatical/Logical Reasoning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mental arithmetic</td>
<td>7</td>
<td>10</td>
<td>70.0</td>
</tr>
<tr>
<td>G</td>
<td>Stroop Colour Test</td>
<td>4</td>
<td>6</td>
<td>66.7</td>
</tr>
<tr>
<td>H</td>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continuous Memory Task, Short Term Memory</td>
<td>4</td>
<td>16</td>
<td>25.0</td>
</tr>
<tr>
<td>I</td>
<td>Sensory Skills</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vigilance Task</td>
<td>9</td>
<td>11</td>
<td>81.8</td>
</tr>
<tr>
<td>J</td>
<td>Attention Task, Continuous Attention Task, Simulated Assembly Line Task</td>
<td>13</td>
<td>16</td>
<td>81.3</td>
</tr>
<tr>
<td>K</td>
<td>Dynamic Visual Acuity</td>
<td>4</td>
<td>4</td>
<td>100.0</td>
</tr>
<tr>
<td>L</td>
<td>Spatial Perception</td>
<td>0</td>
<td>1</td>
<td>0.0</td>
</tr>
<tr>
<td>M</td>
<td>Motor Ability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexterity Test, Finger Tapping</td>
<td>0</td>
<td>5</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Glass Bead Picking Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Physiological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Electroencephalograph (EEG), Continuous EEG, Evoked Potentials, Multiple Sleep Latency Test</td>
<td>18</td>
<td>22</td>
<td>81.8</td>
</tr>
<tr>
<td>O</td>
<td>Actigraphy</td>
<td>2</td>
<td>2</td>
<td>100.0</td>
</tr>
<tr>
<td>P</td>
<td>Subjective Ratings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Profile of Moods Scales</td>
<td>81</td>
<td>99</td>
<td>81.8</td>
</tr>
<tr>
<td></td>
<td>Stanford Sleepiness Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Visual Analogue Rating Scales</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The PIDR value for test sensitivity to sedation (PIDR-SS) was calculated by first deriving the discrimination rate for impairment for a specific test/test group by dividing the number of times that the test/test group was successful in detecting impairment (a), by the total number of times that impairments and no impairments were detected with that test/test group (a+b). The product of this first calculation (a/(a+b)) was then divided by the result of dividing the number of times that all other test groups successfully detected impairments (c), by the total number of times that both impairments and no impairments (d) were detected (c+d).

A high PIDR-SS value represents a greater sensitivity of the test/test group for CNS sedation. Similarly, if a group of tests are not sensitive, then the PIDR-SS will have a value closer to zero. The statistical significance of the PIDR-SS is again calculated using the $X^2$ test on 1 degree of freedom (with Yate's correction).

Table 2.13 lists the calculated PIDR-SS values for the various groups of tests. The calculation of a PIDR-SS and its statistical significance allowed the selection of those tests which were deemed to be most sensitive to the central effects of AHs.
Table 2.13: Discrimination rate of impairment (PIDR-SS) with 1st generation AHs used as positive internal controls in all studies

<table>
<thead>
<tr>
<th>Description of Test</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>PIDR-SS</th>
<th>X²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor Performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual Car Driving, Simulated Car Driving (A)</td>
<td>14</td>
<td>0</td>
<td>257</td>
<td>94</td>
<td>1.37</td>
<td>3.97*</td>
</tr>
<tr>
<td>Psychomotor Speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choice Reaction Time, Simple Reaction Time (B)</td>
<td>45</td>
<td>7</td>
<td>226</td>
<td>87</td>
<td>1.20</td>
<td>4.07*</td>
</tr>
<tr>
<td>Sensorimotor Coordination Speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adaptive Tracking, Continuous Tracking, Critical Tracking, Pursuit Rotor, Simulated Car Tracking, Visuo-Motor Coordination (C)</td>
<td>28</td>
<td>8</td>
<td>243</td>
<td>86</td>
<td>1.05</td>
<td>0.30 (ns)</td>
</tr>
<tr>
<td>CNS Arousal &amp; Information Processing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical Flicker Fusion (D)</td>
<td>17</td>
<td>10</td>
<td>254</td>
<td>84</td>
<td>0.84</td>
<td>1.36 (ns)</td>
</tr>
<tr>
<td>Digit Symbol Substitution Task, Letter Cancellation, Visual Search Task (E)</td>
<td>25</td>
<td>19</td>
<td>246</td>
<td>75</td>
<td>0.74</td>
<td>6.95*</td>
</tr>
<tr>
<td>Grammatical/Logical Reasoning</td>
<td>7</td>
<td>3</td>
<td>264</td>
<td>91</td>
<td>0.94</td>
<td>0.01 (ns)</td>
</tr>
<tr>
<td>Mental arithmetic (F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop Colour Test (G)</td>
<td>4</td>
<td>2</td>
<td>267</td>
<td>92</td>
<td>0.90</td>
<td>0.01 (ns)</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous Memory Task, Short Term Memory (H)</td>
<td>4</td>
<td>12</td>
<td>267</td>
<td>82</td>
<td>0.33</td>
<td>18.62*</td>
</tr>
<tr>
<td>Sensory Skills</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vigilance Task (I)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention Task, Continuous</td>
<td>9</td>
<td>2</td>
<td>262</td>
<td>92</td>
<td>1.11</td>
<td>0.05 (ns)</td>
</tr>
<tr>
<td>Attention Task, Simulated Assembly Line Task (J)</td>
<td>13</td>
<td>3</td>
<td>258</td>
<td>91</td>
<td>1.10</td>
<td>0.13 (ns)</td>
</tr>
<tr>
<td>Dynamic Visual Acuity (K)</td>
<td>4</td>
<td>0</td>
<td>267</td>
<td>94</td>
<td>1.35</td>
<td>0.70 (ns)</td>
</tr>
<tr>
<td>Spatial Perception (L)</td>
<td>0</td>
<td>1</td>
<td>271</td>
<td>93</td>
<td>0.00</td>
<td>0.31 (ns)</td>
</tr>
<tr>
<td>Motor Ability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexterity Test, Finger Tapping Glass Bead Picking Task, Pegboard (M)</td>
<td>0</td>
<td>5</td>
<td>271</td>
<td>89</td>
<td>0.00</td>
<td>10.94*</td>
</tr>
<tr>
<td>Physiological</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electroencephalograph (EEG), Continuous EEG, Evoked Potentials, Multiple Sleep Latency Test (N) Actigraphy (O)</td>
<td>18</td>
<td>3</td>
<td>253</td>
<td>90</td>
<td>1.11</td>
<td>0.34 (ns)</td>
</tr>
<tr>
<td>Subjective Ratings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profile of Moods Scales, Stanford Sleepiness Scale, Visual Analogue Rating Scales (P)</td>
<td>81</td>
<td>18</td>
<td>190</td>
<td>76</td>
<td>1.15</td>
<td>4.07*</td>
</tr>
</tbody>
</table>

a: Number of times that 'impairment' was detected with a specific test group;
b: Number of times that 'no impairment' was detected with the specific test group;
c: Number of times that 'impairment' was detected by all other test groups;
d: Number of times that 'no impairment' was detected with all other test groups.

* = Significant at the 5% level when $X^2$ is equal to or greater than 3.84
Car Driving Tests

Tests of car driving, whether it is actual highway driving, or a simulated car driving task, detected impairments consistently in 14 out of 14 instances. Actual car driving tests (Betts et al 1984, Betts et al 1988, Brookhuis et al 1993, O’Hanlon 1988, Ramaekers & O’Hanlon 1994, Vermeeren & O’Hanlon 1998, Volkerts et al 1994) were used for a total of 9 times and, in all studies, sedation was successfully measured as impairment of standard deviation of lateral position (SDLP). These groups of tests achieved a PIDR-SS of 1.38 which was statistically different to the other groups of tests ($X^2 = 3.97, p<0.05$), suggesting that these tests may be useful in investigating the central effects of AHs. However in all these tests, the parameter under investigation was the ability of the driver to control weaving of the car, measured as the ‘standard deviation from lateral position’ (SDLP), which has been suggested to be an indicator of drug-induced sedation (O’Hanlon 1988, Ramaekers & O’Hanlon 1994, Vermeeren & O’Hanlon 1998).

According to the hierarchical structure of the driving task proposed by Janssen (1979) however, tests of car driving in which the parameter under investigation is the SDLP should be assigned exclusively to the lowest hierarchical level, i.e. the control level, since only the course-keeping tasks are evaluated and important functions such as attention, judgement and co-ordination are not assessed (Willumeit et al 1993). Car driving tests are not a suitable choice for children and non-driving patients and steering is a robust skill, which resists impairment even with high blood alcohol concentrations. Car driving is an acquired skill and despite impairments, an experienced driver can overcome and compensate for this effect. Furthermore, actual car driving tests are logistically, financially and methodologically difficult to establish and control within a crossover protocol employed in most AHs studies.

In addition to tests of psychomotor performance (actual & simulated car driving tests),
the dynamic visual acuity test and actigraphy achieved a 100% discrimination rate, however in both cases, the calculation was based on few instances where the tests were utilised. In addition, when compared to the other groups of tests, these tests failed to achieve a statistically significant PIDR-SS.

Of the many different categories of tests, psychomotor performance tests, measures of reaction time and subjective rating scales achieved significant PIDR-SS values to warrant the selection of these tests as ‘sensitive measures’ when investigating the central effects of AHs (table 2.13).

**Reaction Time**

Tests of reaction time including choice reaction time and simple reaction time were commonly utilised in many studies. In studies with the first generation AHs, these tests were used for a total of 52 times, in which impairments were detected in 45 instances (86.5%), resulting in a PIDR-SS of 1.20 ($X^2 = 4.07$, $p<0.05$).

Choice reaction time is used as an indicator of sensorimotor response, assessing the efficiency of attentional and response mechanisms in the information processing chain without the need for extended cognitive processing (Hindmarch 1980). Measurements of CRT provide information on the constant, very rapid adjustments that individuals must make to their environment, which require them to attend to several potential stimuli at once (Hindmarch 1980, Sherwood & Kerr 1993). This suggests that there is a high degree of construct validity inherent in reaction time measures. The sensitivity of this test is highlighted by the fact that it is one of few tests, which detected impairments with second generation AHs such as mizolastine, loratadine and terfenadine (Shamsi & Hindmarch 1999a, Ramaekers & O’Hanlon 1994, Vuurman et al 1994).
**Sensori-motor Coordination**

Measures of sensorimotor coordination such as adaptive tracking, critical tracking task and visuo-motor achieved a discrimination rate of 78%. However these measures failed to reach statistical significance when compared to the other groups of tests. This is ascribed to the fact that they are not used frequently and thus the cell frequencies are reduced in the calculation of a PIDR-SS for these tests. Furthermore, different methodologies are applied in different laboratories and the lack of standardisation contributes to the lack of impairments detected.

**Critical Flicker Fusion**

Another task, which is commonly featured in studies investigating the central effects of AHs, is the critical flicker fusion (CFF) task. CFF appears in numerous studies with 14 AHs including all the second-generation antihistamines. The discrimination rate with CFF is shown to be 63% but the calculated PIDR-SS failed to reach statistical significance. This value is perhaps lower than expected given the known sensitivity of this measure with psychoactive drugs in general (Hindmarch 1982, Wittenborn 1979) and may be ascribed to the different methodologies involved in measuring the CFF (monocular versus binocular viewing, foveal versus peripheral measurement,) as well as different analysis methods such as method of limits, forced choice, or method of adjustment. However, despite the variation, CFF demonstrated the reduction in cognitive capacity following the administration of first generation AHs (17 out of 27). CFF is one of the most commonly used tasks in the area and has proved sensitive to a wide range of compounds (Smith & Misia 1976, Hindmarch 1981, Hindmarch 1982, Grunberger et al 1982). The advantages of CFF include the simple, non-invasive nature of the test, the
short duration of the assessment, and an absence of major practice effects (subject to training the subjects prior to participation in the study), (Parkin et al 1997).

Memory
The detection rate for impairment of memory following traditional AHs was somewhat low in memory tests (4:16). This finding is in agreement with previous literature (Curran et al 1998, Hindmarch & Bhatti 1987, Hindmarch & Easton 1986, Unchem et al 1986) in which it has been demonstrated that memory is not affected following the use of AHs. The highly significant statistic confirms the lack of sensitivity of these tests when investigating the CNS effects of AHs.

Miscellaneous tests
Of the remaining tests, measures of CNS arousal and information processing such as the digit symbol substitution task, logical reasoning, mental arithmetic and the Stroop colour test as well as attention/vigilance tasks achieved relatively high discrimination rates ranging between 57% for the DSST and 82% for attention and vigilance tasks. However, once again these measures failed to reach statistical significance when compared to the other groups of tests, which may be ascribed to the fact that they are not used frequently and that the lack of standardisation contributes to the lack of impairments detected. Physiological measures such as the EEG achieved high discrimination rates, however such measures are not utilised frequently as the use of these tests is time consuming, expensive and requires specialised personnel. Measurement of motor ability using a variety of tests such as finger tapping and dexterity tests were only used very rarely and thus can not be relied upon to provide useful data.
Continuously Assessment of Activity with Actigraphy

One well-known problem with the use of performance-based measures in psychopharmacology is that individuals can compensate for the effects of a psychoactive compound by changing their performance strategy and/or motivation levels. Performance testing is often intermittent and subjects are usually forewarned or aware of the experimental protocol and the impending test. This allows subjects to prepare themselves for the testing and therefore the limited period of concentration required may not accurately reflect typical levels of alertness throughout the day (Walsh et al 1992, Alford et al 1989).

One way of overcoming the problems associated with the use of fixed test intervals is to use actigraphy to monitor behaviour throughout the day. Actigraphy provides a continuous measurement of the motor component of behaviour (Stanley 1997, Stanley et al 1997) and is thus able to detect impairments in performance throughout the day. Due to its recent introduction in the field of psychopharmacology, actigraphy was only used in two instances, however it successfully detected sedation in both studies. Further research is therefore required with actigraphy in the investigation of the central effects of AHs.

Subjective Assessments

In addition to objective measures of performance, subjective reports were also frequently utilised, demonstrating high discrimination rates (82%). Furthermore, the highly significant PIDR value ($X^2 = 4.07, p<0.05$) differentiates this group of tests from the others and indicates that they can provide important information as regards the potential of AHs to cause impairments of cognitive and psychomotor function. However, self-assessments of performance and sleepiness, although commonly used and easy to
administer, are not as straightforward or as reliable as objective measures of sedation. Subjective reports are much more likely to be influenced by transient fluctuations and other factors such as demand characteristics and environmental stimuli than are objective measures of performance (Alford et al 1989, Roehrs et al 1984, Walsh et al 1992). Despite these inconsistencies, if subjective measures are combined with sensitive and reliable objective tests, they can provide useful supportive data, indicating the total impact of an antihistamine on psychological performance.

2.5 Discussion

Findings from this review indicate that when the different sub-groups of tests are compared to one another, there are three groups of tests, which consistently and successfully detect impairments commonly associated with the use of the AHs. These are tests of psychomotor performance (car driving), measures of reaction time and subjective assessments of sedation. It is also abundantly clear that memory tests and tests of motor ability are not sensitive and therefore of no use in detecting impairment and should not be included in psychometric test batteries.

Based on these findings, it was decided to recalculate the PIR values for all the available first and second generation AHs using only the tests which have been shown to be sensitive in detecting impairments with the AHs (table 2.14).

A comparison of table 2.10 and table 2.14 shows that the rank order of the second generation AHs is not affected, when only sensitive psychometrics are used.
Table 2.14: Rank order of currently available AHs using tests which have a proven sensitivity to impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>PIR</th>
<th>$X^2$ with 1 d.f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine</td>
<td>0</td>
<td>19</td>
<td>152</td>
<td>168</td>
<td>0.00</td>
<td>14.50***</td>
</tr>
<tr>
<td>Levocabastine</td>
<td>0</td>
<td>6</td>
<td>152</td>
<td>181</td>
<td>0.00</td>
<td>3.29 (NS)</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>5</td>
<td>63</td>
<td>147</td>
<td>124</td>
<td>0.14</td>
<td>46.45***</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>8</td>
<td>45</td>
<td>144</td>
<td>142</td>
<td>0.30</td>
<td>21.07***</td>
</tr>
<tr>
<td>Loratadine</td>
<td>4</td>
<td>24</td>
<td>148</td>
<td>163</td>
<td>0.30</td>
<td>10.23**</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>14</td>
<td>5</td>
<td>138</td>
<td>182</td>
<td>1.71</td>
<td>5.59**</td>
</tr>
<tr>
<td>Clemastine</td>
<td>19</td>
<td>7</td>
<td>133</td>
<td>180</td>
<td>1.72</td>
<td>7.88**</td>
</tr>
<tr>
<td>Triprolidine</td>
<td>39</td>
<td>9</td>
<td>113</td>
<td>178</td>
<td>2.09</td>
<td>28.28***</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>35</td>
<td>7</td>
<td>117</td>
<td>180</td>
<td>2.12</td>
<td>26.97***</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>15</td>
<td>1</td>
<td>137</td>
<td>186</td>
<td>2.21</td>
<td>14.23***</td>
</tr>
<tr>
<td>Promethazine</td>
<td>13</td>
<td>1</td>
<td>139</td>
<td>186</td>
<td>2.17</td>
<td>11.66***</td>
</tr>
</tbody>
</table>

a: Number of tests which showed no 'impairment' with the named antihistamine;
b: Number of tests which showed 'no impairment' with the named antihistamine;
c: Number of tests which showed 'impairment' with all other AHs in the database;
d: Number of tests which showed 'no impairment' with all other AHs in the database;
NS= Not significant compared to all other AHs in the database;
* = Significant at 5% level when $X^2$ is equal to or greater than 3.84
** = Significant at 1% level when $X^2$ is equal to or greater than 6.64
*** = Significant at the 0.1% when $X^2$ is equal to or greater than 10.83

It is also evident that fexofenadine (PIR value of 0.00, $X^2=14.50$, p<0.001) is the only currently available antihistamine which can claim to be completely free of adverse CNS effects. These findings lend further support to the claim that fexofenadine should be classed as a 'third generation' antihistamine, at least as regards its unique profile of lack of CNS effects.
2.6 Conclusions

It is evident from the findings of this review that all AHs (with the exception of fexofenadine) possess a potential to produce sedation. This potential is a function of histaminergic mechanisms involved in the control of CNS arousal and is more likely to occur with those substances which cross the blood brain barrier.

In order to be able to detect this possible sedative activity, it is important to use a battery of tests which have proved to be sensitive and reliable indicators of sedation.

Although a number of tests failed to achieve a significant PIDR-SS value, if standard methodologies are applied, information processing tasks such as the CFF as well as vigilance and attention tasks are extremely sensitive to the effects of CNS active compounds. Of the tests reviewed in this chapter, measures of reaction time, tests of car driving and subjective assessments were successful in detecting impairment associated with the use of the AHs. These were therefore used to re-calculate the PIR values for all currently available AHs to allow the ranking of these compounds as regards their ability to impair cognitive and psychomotor performance.

It must be appreciated, however that regardless of the choice of a reliable and valid test battery, detection of sedation is in fact directly dependent on the actual presence of sedative effects of the drug. If the sedative effects of AHs are dose related, it is not surprising that even a well designed test battery is unable to detect sedation below their lowest threshold for stimulus detection. In the review, no distinction was made between the different doses of the selected AHs, as a further breakdown into different dosage groups would have resulted in too few tests being available to allow for comparisons between drugs to be made and some tests being used too infrequently to draw any conclusions. In addition, as indicated previously, there is a substantial inter-individual variability with regards to antihistamine induced sedation.
However as indicated in table 2.3, some evidence of sedation could be seen over the full range of doses used with the first generation AHs.

Results obtained from the above described studies support the claim that the newer generation of AHs have a lower index of sedation than their predecessors, although only one can claim to be completely free of sedation regardless of the administered dose.

In view of the above findings, AHs should ideally be divided into three categories (table 2.15).

The first generation AHs such as chlorpheniramine, clemastine, diphenhydramine, hydroxyzine, promethazine and triprolidine which commonly cause impairments of cognitive and psychomotor performance even when administered within the recommended therapeutic dose range; the second generation of AHs with which there is some evidence of sedation, particularly in higher dose regimens (cetirizine, ebastine, loratadine, mizolastine and terfenadine) and a third generation of AHs such as fexofenadine with which there is no evidence of detrimental CNS effects regardless of the administered dose.
Table 2.15: Categorisation of AHs as regards their profile of CNS effects

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>PROFILE OF CNS EFFECTS</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; generation AHs</td>
<td>Commonly caused impairment in dose ranges studied</td>
<td>Chlorpheniramine (4mg-16mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clemastine (1mg-4mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diphenhydramine (25mg-150mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydroxyzine (20mg-50mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Promethazine (10mg-30mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Triprolidine (1.25mg-15mg)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; generation AHs</td>
<td>Some evidence of impairment in dose ranges studies, particularly in higher dose regimens</td>
<td>Cetirizine (2.5mg-20mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ebastine (10mg-30mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loratadine (10mg-40mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mizolastine (5mg-45mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Terfenadine (20mg-240mg)</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; generation AHs</td>
<td>No evidence of impairment in dose ranges studies</td>
<td>Fexofenadine (80mg-240mg)</td>
</tr>
</tbody>
</table>
CHAPTER 3: SUBJECTIVE REPORTS OF SEDATION IN CLINICAL
STUDIES OF ANTIHISTAMINES

3.0 Chapter Outline
This chapter presents a review of the clinical literature, surveying the data on the incidence of subjectively reported sedation in patient studies with AHs. Due to the numerous ways in which inter-study differences can confound and distort attempts of a 'meta-analysis' of clinical trial results, the findings of this review can only be indicative of trends as regards antihistamine-induced sedation and should not be interpreted as an attempt to ascertain the true sedative potential of AHs.

The primary objective of this review is to examine whether patients are able to differentiate between those AHs with pharmacological i.e. obvious and pronounced sedative activities and those which do not possess a pharmacological basis for sedation, but which still engender subjective feelings of drowsiness/tiredness especially when administered at high clinical dose regimens.

3.1 Introduction
Sedation as a drug induced side effect is frequently reported in clinical studies with AHs. The investigation of the incidence of side effects produced by a given treatment draws on the patient as a primary source of information. Patient reports, however, are highly subjective especially when concerning personal experiences of changes in mood, energy levels etc., and the methods used in clinical trials for obtaining this type of information are either generally ill defined or non-existent (Rombaut 1995).

Although a large number of reviews (Haria et al 1994, McTavish 1990, Spencer et al 1993, Wiseman & Faulds 1996) have been conducted with the so-called 'non-sedative'
AHs as regards the incidence of sedation, the conclusions are biased and must be treated with caution. This bias results from the intention of the reviewer to demonstrate that a specific drug dose regimen is not statistically different to placebo and should therefore be labelled as ‘non-sedative’. The reviewing technique includes data only on other AHs, which are included in comparative studies with the drug under investigation. A more neutral approach to conducting a review would be to perform a computer search to include all the available data on the antihistamine in question and all other AHs. Furthermore, as the individual study designs vary and the patient selection criteria are different depending on the requirements of the clinical study protocol, it is apparent that differences between AHs as regards sedation will become evident if a careful selection of studies is made according to the robustness of their underlying experimental methodologies.

3.2 Selection of Studies

A computer-assisted MEDLINE search was conducted to identify clinical studies with AHs, published between 1966 and 1999. Medline search ensured that only studies published in peer-reviewed journals meeting the specific criteria for acceptance were included in the review. As well as publications, data were also included from studies published in abstract format in peer-reviewed journals, so long as the study satisfied the inclusion criteria and the data were presented in a format that clearly indicated the incidence of sedation with each treatment condition. In order to minimise the effect of external factors, a number of strict criteria had to be adhered to in order to be included in the review. Studies had to be conducted under strict double blind conditions, with the aim of investigating the clinical efficacy of one or more AHs. Studies had to be of either a parallel or crossover design. Inclusion criteria required the studies to be placebo-
controlled, in which the number of patients experiencing sedation was documented for each treatment group.

Studies conducted with children, studies in which rescue medication was allowed, or those with single blind designs were all excluded from the review. A selection of studies excluded with reasons for non-inclusion can be found in table 3.1.

For each of the selected studies, the actual number of reports of sedation for each treatment group was listed. Similarly, the number of patients not reporting a sedative effect was calculated by subtracting the number of reports of sedation from the total number of patients receiving each treatment (table 3.2).

The term sedation was used as a collective term to represent all statements referring to a general lowering of CNS activity. These included sedation (Belaich et al 1988, Irander et al 1990), somnolence (Bruno et al 1981, Eisen et al 1988), drowsiness (Blamoutier 1978, Bruno et al 1989), fatigue (Dockhorn et al 1987, Girard et al 1985), tiredness (Gastpar et al 1988, Grant et al 1988), CNS depression (Brandon & Weiner 1982), and sleepiness (Dugue et al 1982, Mellillo et al 1982).

A cursory review of the clinical studies revealed that in most studies, the total number of reports of sedation were provided without any particular indication of the number of patients reporting this effect. Multiple terms were used in certain studies to report the sedation and it was not possible to establish from these studies whether the data referred to one patient experiencing these effects, or if the effect was attributed to a number of patients experiencing this sedation. As it was impossible to resolve this approach, it was assumed that each report of sedation reflected a particular patient.

No distinction was made between the methods used to assess potential sedation.
Table 3.1: A selection of studies excluded from the clinical review of AHs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>REASON FOR EXCLUSION</th>
<th>NO OF STUDIES</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single blind</td>
<td>1</td>
<td>Zuberbier et al 1996</td>
</tr>
<tr>
<td></td>
<td>Combination treatment</td>
<td>1</td>
<td>Du Buske 1995</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.1: A selection of studies excluded from the clinical review of AHs (cont.)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>REASON FOR EXCLUSION</th>
<th>NO OF STUDIES</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clemastine</td>
<td>No placebo</td>
<td>2</td>
<td>Sheriff &amp; Wallace 1976, Todd 1975</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>No placebo</td>
<td>1</td>
<td>Moscati &amp; Moore 1990,</td>
</tr>
<tr>
<td></td>
<td>Combination treatment</td>
<td>2</td>
<td>Majchel et al 1992, Vuurman et al 1996</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>No placebo</td>
<td>1</td>
<td>Nsouli et al 1998</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Incomplete information</td>
<td>1</td>
<td>Wong &amp; Hendeles 1981</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>2</td>
<td>Njaa et al 1992, Bjorksten &amp; Kjellman 1989, Pipkorn et al 1985,</td>
</tr>
<tr>
<td></td>
<td>Incomplete information</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.1:  A selection of studies excluded from the clinical review of AHs (cont.)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>REASON FOR EXCLUSION</th>
<th>NO OF STUDIES</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mequitazine</td>
<td>Placebo</td>
<td>1</td>
<td>Blamoulier 1978</td>
</tr>
<tr>
<td></td>
<td>Incomplete information No</td>
<td>1</td>
<td>Laugier &amp; Orusco 1978</td>
</tr>
<tr>
<td></td>
<td>Combination treatment</td>
<td>2</td>
<td>Backhouse et al 1990a, Kemp et al 1988</td>
</tr>
<tr>
<td></td>
<td>Rescue medication</td>
<td>1</td>
<td>Kagan et al 1980</td>
</tr>
</tbody>
</table>
3.2.1 Proportional Sedation Ratio (PSR)

In order to allow inter-drug comparisons to be made, the sedative properties of one antihistamine were compared with the properties of all other AHs. The procedure employed to calculate a ‘proportional impairment ratio’ for AHs in the previous chapter was applied to this data to enable the calculation of a respective ‘proportional sedation ratio’ (PSR) for each antihistamine. In the calculation of PSR, placebo was included in the analysis as a ‘drug’ condition.

The PSR was expected to show whether the use of an antihistamine is associated with subjectively reported sedation and if so, the extent of that sedation when compared to the sedation produced with all other AHs. The greater the PSR, the greater are the reports of sedation associated with the use of that antihistamine. Conversely, an antihistamine with which there is no subjective reports of sedation would have a PSR value of zero. Those AHs with which reports of sedation increase in response to higher doses, would have PSR values above zero but lower than those which are inherently sedative.

The formula presented in chapter two (figure 2.3) for the calculation of a proportional impairment ratio was adapted to allow the calculation of a PSR for each antihistamine, thereby enabling the ranking of these AHs as regards their potential to produce sedation. The PSR for each antihistamine was calculated by the division of the ‘sedation ratio’ for the specific antihistamine by the ‘sedation ratio’ for all the other AHs in the database. In order to enable the AHs to be ranked as regards their potential produce sedation, the statistical association for each PSR was calculated using the \( \chi^2 \) test on one degree of freedom (with Yates’ correction).
3.3 Results

A total 785 studies were identified by MEDLINE, of which 195 were evaluated for possible inclusion in the review. Of the 195 studies, however, only 77 clinical studies satisfied the criteria for inclusion and were accepted and included in the review. Reports of sedation were not routinely assessed in all studies and so the number of studies, which were subsequently accepted, was dramatically reduced.

Fifty nine of the 77 selected studies were conducted using parallel groups; in the remaining 19 studies, treatments were allocated in crossover designs (table 3.2). Due to the small number of studies adopting a crossover design, the results of both parallel and crossover groups were pooled together.

The clinical indications tested in these studies were seasonal allergic rhinitis (45 studies), seasonal conjunctivitis (1 study), perennial allergic rhinitis (11 studies), common cold (1 study), chronic idiopathic urticaria (18 studies), cold urticaria (1 study) and dermatographia (1 study).

Duration of treatment ranged between 3 days (Krause & Shuster 1984) and 6 weeks (Tanay & Neumann 1989).

Of all the AHs reviewed, terfenadine has been the most extensively studied (33 studies), followed by loratadine (16 studies) and cetirizine (15 studies). A number of AHs included in the review featured only once (cyproheptadine, ebastine, levocabastine, mequitazine and norebastine).

Terfenadine featured in 33 studies with a total of 1917 patients receiving the drug at doses between 20mg and 200mg. In 11 of these terfenadine studies, chlorpheniramine was included in the study as a standard comparator and used in a total of 795 patients at doses ranging between 2mg and 8mg three times daily (t.i.d.).
Loratadine was compared with placebo in a total of 16 studies, of which 5 included terfenadine as a positive control for efficacy. Loratadine was administered as a 10mg once daily (o.d.) dose in 14 of these studies and in two studies, a 40mg dose was administered. Of a total of 1095 patients receiving loratadine, 97 reported sedative side effects.

Cetirizine was compared with placebo in a total of 15 studies, of which 4 included terfenadine as a positive control for efficacy. Cetirizine was administered at doses ranging between 10mg o.d. to 40mg o.d., of which 10 studies investigated the effects of higher doses of cetirizine (10mg & 20mg). Of the 1112 patients receiving cetirizine, 190 patients reported sedative side effects.

Due to its recent introduction, the number of clinical studies performed with fexofenadine was low, although within these four studies, 658 patients were administered a dose of fexofenadine ranging from 60mg o.d. to 240mg b.d.

Three of these studies were placebo controlled with no comparator included in the study design, although to date, one study has compared the effects of fexofenadine with loratadine (Day et al 1997). Of the 658 patients receiving a dose of fexofenadine up to 240mg, there were no reports of sedation in any of the four clinical studies.

Astemizole was investigated in 9 clinical studies, in which a 10mg dose was administered to 191 patients. Astemizole at a dose of 10mg produced sedation in 17 patients.

Acrivastine was administered to 258 patients in 8 clinical studies and the use of acrivastine was associated with 37 reports of sedation.

Seven clinical studies investigated the effects of hydroxyzine in a total of 258 patients. The use of hydroxyzine was associated with significant reports of sedation (141 reports).
Table 3.2: Clinical studies with AHs in which reports of sedation were documented

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DRUG CONDITION</th>
<th>CORRESPONDING ‘PLACEBO’ CONDITION</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NORS</td>
<td>NRONS</td>
<td>NROS</td>
</tr>
</tbody>
</table>

NORS = Number of reports of sedation
NRONS = Number of reports of no sedation
<table>
<thead>
<tr>
<th>DRUG</th>
<th>DRUG CONDITION</th>
<th>DRUG 'PLACEBO' CONDITION</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NORS</td>
<td>NRONS</td>
<td>NORS</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>12</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Ebastine</td>
<td>3</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>0</td>
<td>658</td>
<td>0</td>
</tr>
<tr>
<td>Levocabastine</td>
<td>2</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Mequitazine</td>
<td>0</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Norebastine</td>
<td>9</td>
<td>179</td>
<td>3</td>
</tr>
</tbody>
</table>

NORS = Number of reports of sedation
NRONS = Number of reports of no sedation
Table 3.2: Clinical Studies with AIs in which reports of sedation were documented (cont.)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DRUG CONDITION</th>
<th>NRS</th>
<th>NRNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terfenadine</td>
<td></td>
<td>167</td>
<td>1718</td>
</tr>
</tbody>
</table>

NRS = Number of reports of sedation
NRNS = Number of reports of go sedation
To allow a comparison between AHs investigated in this review, the total number of reports of sedation was expressed as a percentage of patients receiving each antihistamine (table 3.3).

These indices of sedation demonstrated that that the second generation AHs with the exception of cetirizine were not significantly different to placebo, and in sharp contrast with the traditional AHs as regards the incidence of subjectively reported sedation.

Table 3.3 Percentage of ‘sedation’ reported by patients treated with various dose regimens of different AHs

<table>
<thead>
<tr>
<th>ANTIHISTAMINE</th>
<th>PERCENTAGE SEDATION (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine</td>
<td>0.00</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.46</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>8.86</td>
</tr>
<tr>
<td>Loratadine</td>
<td>8.86</td>
</tr>
<tr>
<td>Astemizole</td>
<td>8.90</td>
</tr>
<tr>
<td>Levocabastine</td>
<td>10.00</td>
</tr>
<tr>
<td>Acrivastine</td>
<td>14.50</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>17.00</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>25.60</td>
</tr>
<tr>
<td>Clemastine</td>
<td>33.70</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>53.60</td>
</tr>
</tbody>
</table>

* The calculated percentage of sedation with fexofenadine is zero because there were no reports of sedation with fexofenadine.

In as much this provided the means to categorise the AHs as those which have obvious sedative properties, from those which are non-sedating within their dose regimen, this measure does not reflect a true scenario, as the effects of a specific antihistamine were considered in isolation and without a reference to the properties of all other AHs.
Therefore in order to make inter-drug comparisons, the PSR for each antihistamine was calculated using the previously described formula outlined in chapter two.

Table 3.4 lists the PSR values for all the AHs used in this clinical review.

It is evident from these studies which, within the limitations of clinical investigations, are considered to be the most adequately controlled, that the use of most AHs are commonly associated with reports of sedation. The incidence of reported sedation is greater with the first generation AHs that are known to possess sedative properties. The calculated PSR values reflect these finding in that chlorpheniramine, clemastine and hydroxyzine achieved highly significant PSR values in excess of 2, whereas the second generation AHs with the exception of cetirizine were all very close to the calculated PSR of placebo.
Table 3.4  Proportional Sedation Ratio (PSR) for all AHs in the review

<table>
<thead>
<tr>
<th>Drug</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>PSR</th>
<th>X² with 1 d.f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine</td>
<td>0</td>
<td>658</td>
<td>1517</td>
<td>9032</td>
<td>0.00</td>
<td>108.2***</td>
</tr>
<tr>
<td>Mequitazine</td>
<td>0</td>
<td>23</td>
<td>1517</td>
<td>9667</td>
<td>0.00</td>
<td>2.54 (NS)</td>
</tr>
<tr>
<td>Norebastine</td>
<td>9</td>
<td>179</td>
<td>1508</td>
<td>9511</td>
<td>0.35</td>
<td>11.76***</td>
</tr>
<tr>
<td>Placebo</td>
<td>324</td>
<td>3507</td>
<td>1193</td>
<td>6183</td>
<td>0.52</td>
<td>127.63***</td>
</tr>
<tr>
<td>Astemizole</td>
<td>17</td>
<td>174</td>
<td>1500</td>
<td>9516</td>
<td>0.65</td>
<td>3.57 (NS)</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>167</td>
<td>1718</td>
<td>1350</td>
<td>7972</td>
<td>0.61</td>
<td>41.87***</td>
</tr>
<tr>
<td>Loratadine</td>
<td>97</td>
<td>998</td>
<td>1420</td>
<td>8692</td>
<td>0.63</td>
<td>22.69***</td>
</tr>
<tr>
<td>Levocabastine</td>
<td>2</td>
<td>18</td>
<td>1515</td>
<td>9672</td>
<td>0.74</td>
<td>0.21 (NS)</td>
</tr>
<tr>
<td>Acrivastine</td>
<td>37</td>
<td>221</td>
<td>1480</td>
<td>9469</td>
<td>1.06</td>
<td>0.08 (NS)</td>
</tr>
<tr>
<td>Ebastine</td>
<td>3</td>
<td>16</td>
<td>1514</td>
<td>9674</td>
<td>1.17</td>
<td>0.08 (NS)</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>190</td>
<td>922</td>
<td>1327</td>
<td>8768</td>
<td>1.30</td>
<td>12.96***</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>218</td>
<td>634</td>
<td>1299</td>
<td>9056</td>
<td>2.04</td>
<td>113.30***</td>
</tr>
<tr>
<td>Clemastine</td>
<td>202</td>
<td>398</td>
<td>1315</td>
<td>9292</td>
<td>2.72</td>
<td>217.68***</td>
</tr>
<tr>
<td>Brompheniramine</td>
<td>98</td>
<td>96</td>
<td>1419</td>
<td>9594</td>
<td>3.92</td>
<td>227.46***</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>141</td>
<td>122</td>
<td>1376</td>
<td>9568</td>
<td>4.26</td>
<td>366.08***</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>12</td>
<td>6</td>
<td>1505</td>
<td>9684</td>
<td>4.96</td>
<td>39.06***</td>
</tr>
</tbody>
</table>

a: Number of reports of 'sedation' with specific antihistamine;  
b: Number of reports of 'no sedation' with specific antihistamine;  
c: Number of reports of 'sedation' with all other AHs;  
d: Number of reports of 'no sedation' with all other AHs.  

NS = Not Significant  
* = Significant at 5% level when X² is equal to or greater than 3.84  
** = Significant at 1% level when X² is equal to or greater than 6.64  
*** = Significant at the 0.1% when X² is equal to or greater than 10.83

The PSR value of cetirizine appears high when compared with the other second generation AHs. The studies with cetirizine demonstrate that there were 190 reports of sedation in a total of 1112 patients receiving cetirizine. However a closer examination of the data reveals that of the 15 studies, higher doses of 20mg & 40mg were investigated in 10 studies. In comparison, all studies with astemizole investigated the effects of this
antihistamine at its recommended dose of 10mg. With loratadine, of the 16 studies employed in the investigation of its clinical efficacy, 14 were conducted with 10mg dose of loratadine.

This therefore provides an explanation for the high PSR value obtained with cetirizine and highlights the problems of drug comparisons across their various dose regimens. A better methodology would be to compare clinically equivalent doses of AHs. However, the number of studies with these AHs in which subjective reports of sedation are adequately assessed and reported is very limited and therefore 'dose equivalent' comparisons are not possible.

Although the calculated PSR value of loratadine is low and close to that obtained with placebo, these comparisons are made with loratadine at doses at which the drug is known to be free of sedative effects. Objective evidence of CNS impairment as well as subjective reports of sedation have demonstrated the detrimental CNS effects of loratadine at doses above 10mg (Gaillard et al 1988, Riedel et al 1990, Shamsi & Hindmarch 1999a). It is highly unlikely that loratadine would maintain its low PSR value if data with higher doses of the drug were included.

Due to its recent introduction, fexofenadine has not been so extensively studied in clinical trials. Although a large number of trials have been conducted to assess its efficacy, the number of placebo controlled studies in which sedation has been assessed is low. To date, fexofenadine at doses up to 240mg has been administered to 658 patients and within the dose ranges studied, it is demonstrably free from any sedative activity.
3.4 Discussion and Conclusions

In this chapter the overall incidence of sedation in patients receiving the first generation AHs was high with PSR values in excess of two indicating the significance of such findings. Sedation reported following the administration of the second generation AHs was lower in comparison to the traditional AHs, with PSR values between 0.35 and 1.30. There appears to be great variability as regards the subjective reports of sedation with these AHs. Subjective reports of sedation were absent following the administration of fexofenadine and of lower frequency with terfenadine and loratadine and the greatest following the administration of cetirizine.

This finding is contrary to the rankings obtained with these AHs in experimental studies with healthy volunteers.

The high incidence of sedation reported with cetirizine is explained by the fact that most studies investigating the effects of cetirizine were conducted with doses of cetirizine in excess of 10mg. In contrast, 14 out of the 16 studies investigating the effects of loratadine were performed with loratadine at its recommended dose of 10mg.

The CNS impairing effects of loratadine which have been previously documented may have been masked in these clinical studies as a result of the administration of lower doses.

Despite the absence of precise methods and measures and adequate controls in clinical studies with AHs, the results of the present review confirm that, in terms of sedation, patients are able to distinguish between placebo and the older, sedative H1 receptor antagonists such as chlorpheniramine, clemastine and hydroxyzine. On the other hand, with the second generation AHs (terfenadine, loratadine, and cetirizine), the patients' experiences of sedative effects were lower and not dissimilar to placebo in most cases.
Two explanations are provided as to why patients' discrimination of sedation were successful.

The first factor, which may influence the patients' detection of sedation, is related to the symptomatology of the allergic disorders. It is well recognised that allergic rhinitis, may produce a degree of drowsiness (Spaeth et al 1996, Bousquet et al 1994). Relief of rhinitis symptoms may therefore alleviate the accompanying drowsiness.

As a non-active treatment, placebo does not pharmacologically modify the histamine receptor and as such is not able to alleviate the symptoms of the allergic disorder. It is, however, accepted that placebo does in certain patient populations exert a 'clinical placebo' effect, whereby the patient feels relieved of the symptoms of the disorder, despite the fact that the treatment is not pharmacologically active (Craen et al 1999). This 'placebo' effect, however, is not experienced by all and it is possible that due to lack of pharmacological modification of the receptor, the patient does not experience any relief from allergic symptomatology and consequently the incidence of sedation is not reduced. As a result of the persisting sedation, the patient's ability to differentiate between an active treatment and placebo may therefore be enhanced and indirectly affect the outcome.

The second factor is related to the principle criterion for inclusion of studies in this review. This required the studies to be of a double blind and placebo-controlled design. However, as with all clinical studies, the degree to which patients are blinded to active or placebo treatment is questionable. This argument holds true especially for those AHs, which produce a relatively fast and easily recognisable effect. AHs generally work within a few days and it is possible that patients realised when they were randomised to receive placebo as a result of persistent symptomatology.
Depending upon the explanations provided by the treating physician, their ability to recognise sedation may have been further enhanced. It therefore appears that with clinical, as with experimental studies, the inclusion of a positive control may be prove to be beneficial.

The findings from this review therefore broadly confirm that patients do experience sedation with certain AHs. Despite the lack of standardisation of methods in these clinical studies, the methodology used to calculate a PSR for each antihistamine appears to be successful in demonstrating differences between AHs.
CHAPTER 4: METHODS & MEASURES USED TO INVESTIGATE ANTIHISTAMINE INDUCED PERFORMANCE IMPAIRMENT

4.0 Chapter Outline

A review of the effects of AHs on measures of behaviour in both healthy volunteers and patient populations in chapters two and three concluded that even amongst the new and so called non-sedative AHs, only a few can claim to be effectively free of sedative side effects even when administered at doses recommended by the manufacturer.

It is also evident that only a few tests can reliably discriminate between the different AHs as regards their effects on measures of performance. With this in mind, this chapter discusses the general methods and measures employed in each of the experiments. Descriptions of selected tests are given, along with evidence of their validity and reliability. The common procedures adopted are outlined, including subject selection, study conduct, experimental design and statistical management of data. The study specific procedures are outlined in chapter 5.

4.1 Introduction

The findings from the previous two chapters demonstrate that, in the study of the effects of AHs on performance, when the findings from all studies are all pooled together, general patterns of effect become apparent, confirming that the second generation of AHs have both a much more favourable therapeutic index than their predecessors and a much better side effect profile.

Discrepancies do exist however between the findings of individual investigations. These may be explained in terms of different testing methodologies, and also the fact that a
diverse range of tests are adopted by different groups. Study designs differ between research centres and study protocols are not standardised between research groups.

The literature is replete (Hindmarch & Shamsi 1999, Meltzer & Welch 1996, Passalacqua et al 1996, Rombaut & Hindmarch 1994, Seppala et al 1981, Simons et al 1996, Simons et al 1999, Witek et al 1995) with studies comparing the various methods of assessment of sedative effects, yet the greater sensitivity of one particular method over another has yet to be absolutely demonstrated. It is becoming increasingly important to use psychometric tests which are valid, reliable and sufficiently sensitive to detect minimal changes in cognitive functioning and psychological status. Failure to detect sedative effects using objective psychometrics, even though subjective evidence of sedation existed, has been reported in a variety of studies (Hughes & Forney 1964, Baugh & Calvert 1977, Moser et al 1978, Kulshrestha et al 1978, Pishkin et al 1983).

As discussed in chapter 2, an appropriate model of information processing should be adopted in order to assess the effects of AHs on psychological aspects of behaviour. Furthermore, it is imperative that the tests are carefully selected to allow differentiation between types of impairment on the various cognitive and psychomotor aspects of behaviour.

It is evident, however, that there are many aspects to a behavioural response and therefore different testing strategies are utilised by different research groups, resulting in the use of many tests which are not reliable or valid indicators of CNS effects.

A review by Hindmarch (1980) found that many of the tests used in psychopharmacology lacked a history of reliability and validity and were unlikely to provide useful data.

Reliability is often defined as the consistency of scores obtained by the same person when re-examined with the same test on different occasions. This concept involves the estimation of the error of measurement of a single score, making it possible to predict the
range of fluctuation likely to occur as a result of chance factors (Parrott 1991a). Having considered the reliability of a test, it is thereby possible to establish whether differences occurring in test scores are attributable to real differences or to test error. The validity of a test reflects the ability of a particular test to measure a specific component of behaviour/state against independently obtained data for that component, thereby indicating how well the test actually measures the particular component under investigation. Reliability involves the value of the task as a predictor of the impairment potential and validity involves the significance of the actual result obtained (Parrott 1991b).

In addition to the availability of a wide variety of psychometric tests, certain popular tests are performed in various different ways. For example, the critical flicker fusion task, although a very popular measure, is performed in a number of different ways—monocular versus binocular viewing, foveal versus peripheral measurement (Hindmarch 1987, Frewer & Lader 1993).

Bobon et al (1982) stated that discrepancies in results with the same drug may be largely due to the differences in the methods of measuring CFF, but goes on to say that CFF is a “valid and economical test of sedation versus alertness” and that if certain criteria are met, then CFF can provide a reliable measure of central processing capacity. Despite complying with the pre-requisites for a standardised test battery, inadequate consideration of the moderator variables may also undermine the clinical relevance of the test results and thus influence the outcome. These variables arise through the use of a test in a particular population, errors possibly emanating from factors such as age, sex, health status, personality and sociocultural effects etc. Therefore in order to obtain reproducible results, a number of factors need to be taken into consideration when designing a study.
The most important aspect of a study design is that the tests should be selected carefully according to a well defined behavioural model. The tests should be easy to understand and perform by the subject and easy to administer, score, and interpret for the experimenter. The administration of the test should be standardised with regard to the equipment and methods employed and the environment in which the test is executed, with specific emphasis on minimising levels of distraction. Importance should also be placed on the maintenance of the order of testing sequence when more than one test is being utilised.

It is also important that the tests are administered by trained experimenters and that the volunteers are appropriately trained on the test batteries to preclude any learning effects (Parkin et al, 1997). Differences in instructions given to subjects may profoundly affect performance. The amount of help given by the experimenter should always be defined in order to achieve efficient standardisation.

The adoption of double blind experimental design ensures that neither the subject nor the experimenter is aware of the treatment regimen. Inclusion of a verum (positive control) is imperative in order to validate the results as a drug effect may be masked by the nature of the task itself. The inclusion of a verum also ensures the sensitivity of the tests to the drug effects at that particular time. All the experiments within this thesis included a verum condition in which the vera (e.g. promethazine, triprolidine) have all been previously shown to impair cognitive and psychomotor performance (Hindmarch et al 1999, Kerr et al 1994, Shamsi & Hindmarch 1999a, Shamsi & Hindmarch 1999b, Stone et al 1999).

Motivational factors may also influence the results. The motives of the volunteers can be classified as financial, spiritual and psychological. The intentions of the volunteers, the payment or privileges afforded them and the expectations of both subject and
experimenter can directly influence the results obtained (Ayd 1972). The process of
direct monitoring is thought to instil sufficient motivation to enhance performance,
irrespective of the actual test employed (Fraser 1953). However the motivation inherent
in the task situation may also be an important factor in influencing performance, the
impairing nature of the drug on performance being camouflaged by the stimulatory nature
of the task.

The effect opposing motivation is the concept of boredom. Diminished performance
efficiency is usually associated with the boredom that results from a dull, monotonous
and repetitive performance task (O’Hanlon 1981). The search to establish a compromise
between the two effects is imperative if validation is to be achieved.

Both culture and lifestyle can influence a person’s perception of effects such as sedation.
This has been highlighted by Rombaut et al (1986) for tests of psychomotor performance.
Sociocultural effects must also be considered to determine whether particular symptom
states are of sufficient importance to merit complaint. Different cultures often vary in
their interpretation of side effects, an admission often being akin to confessing a
weakness.

Volunteers should be selected carefully to ensure that they are healthy and not taking any
concomitant medication (including social substances such as caffeine, alcohol and
nicotine), as both illness and the use of medication can confound results and therefore
affect the outcome of the study. All studies described in this thesis employed adequate
screening procedures to exclude the use of any concomitant medication, alcohol etc and
to ensure that volunteers and patients fulfilled the relevant inclusion/exclusion criteria.
A firm conclusion about whether one drug represents an improvement over another in
terms of CNS impairment requires concurrent evaluation with peripheral effects. This
provides evidence as to whether differences between compounds in sedative potential are
not simply due to differences in dose (Levander et al 1985). It is often recommended to extend the range of dosages beyond that employed therapeutically in order to ascertain at what dosage CNS effects become evident. A new H₁-receptor antagonist may be found to be devoid of CNS effects purely because it is used at a dose that induces only a weak H₁ inhibitory effect. Of paramount importance is the balance between the desired peripheral effect and the undesired CNS effects.

All of the above have been taken into consideration where applicable, in the design of the experiments which are described in this thesis. The following section is a description of the measures employed to evaluate the effects of AHs on various measures of cognitive function and psychomotor performance.

4.2 Measures

It is widely accepted that many of the tests used in psychopharmacology lack a history of validity and reliability (Hindmarch 1980, Parrott 1991a, 1991b, 1991c). In order to produce meaningful results, a battery of tests should be used which have been shown to be reliable, valid and sensitive to the effects of psychoactive drugs. It is imperative that the tests should be able to discriminate between drugs in the same class, as well as differentiating between different doses of the same drug.

Since the 1970s, research at the HPRU has centred on a battery of tests, which have been shown to be reliable indicators of drug action. To date, this approach has been used to profile over 200 different psychoactive compounds in both healthy volunteers and patient populations. Their validity, sensitivity and reliability has been demonstrated using a wide variety of psychoactive compounds at various doses (Hindmarch 1975, 1980, Parrott 1982, Sherwood & Kerr 1993). Over the years the tests have been computerised and so stimulus presentation and recording of results are now controlled automatically, thereby
allowing accurate data collection. Inter-test variability is reduced by utilising the same systems across studies and as the data is collected electronically, the results are devoid of human error, thus increasing the reliability of the utilised tests. Due to the proven sensitivity, reliability and validity of these tests, it was decided to incorporate these in the experimental design in order to facilitate the assessment of the effects of AHs on various aspects of information processing.

The core batteries of tests consist of Critical Flicker Fusion (CFF), Choice Reaction Time (CRT), Sternberg Memory Scanning task (SMST) and Compensatory Tracking Task (CTT). Line Analogue Ratings for Sedation (LARS) is used to assess subjectively overall ratings of sedation and the Leeds Sleep Evaluation Questionnaire (LSEQ) is used to subjectively assess various aspects of sleep. Other tests are also used in various experiments and these include Actigraphy (ACT), Cognitive Failures Questionnaire (CFQ), Milford Memory Test (MMT), Hamilton Anxiety Rating Scale (HARS), Digit Span (DS) and Clinical Global Impressions (CGI).

In addition to the psychometric test battery, the weal and flare test was used in experiments 1 & 2 to assess the ability of a number of second generation AHs to inhibit the weal and flare reaction - a standard method used to assess the efficacy as well as the potency of AHs.

4.2.1 Main Test Battery

Critical Flicker Fusion (CFF)

CFF has been used as a research tool for many years with interest in CFF dating back to the 18th century (Landis, 1953). CFF is regarded as the assessment of choice for investigating the change in overall integrative capacity of the CNS, the state of arousal, mental alertness and cognitive potential. CFF has been referred to as ‘valid and
A measure of sedation versus alertness which 'can be reliable if certain variables are taken into account' (Bobon 1982).

Despite the variety of experimental equipment available (monocular versus binocular viewing, foveal versus peripheral measurement) and different methods of measurement (method of limits, forced choice, method of adjustment), the literature shows a remarkable consistency in the observed effects of psychoactive drugs (Hindmarch 1982).

Critical flicker frequency is defined as the point at which a flickering light gives rise to the subjective sensation of a steady light and fusion frequency is the opposite of this, i.e. the point at which steady light is perceived as a flickering light. Within the information processing model, CFF is defined as the ability to process discrete 'bits' of information (Hindmarch 1980, Hindmarch 1982).

An increase in CFF threshold is thus indicative of CNS arousal, whereas a reduction in the threshold is associated with a decrease in information processing capacity and therefore a decline in the overall cognitive ability.

The advantages of the measure include the simple, non-invasive nature of the test, the short duration of the assessment (approximately two minutes) and an absence of major practice effects (Parkin et al 1997).

Although there are no agreed experimental techniques for the measurement of CFF, the 'method of limits' is the most frequently used. Several researchers have reviewed the use of CFF in psychopharmacology (Turner 1968, Smith & Misiak 1976, Hindmarch 1982), and have concluded that if standardised methods are adopted, CFF can be a useful research tool in investigating the action of drugs on the CNS.

All CFF measurements were made using the Leeds Psychomotor tester (Hindmarch 1975, Hindmarch & Parrott 1978, Hindmarch & Subhan 1983). With subjects sitting at a distance of one meter facing the CFF test apparatus, four light emitting diodes flicker on
and off at a 50/50 light-dark ratio according to a square waveform at a constantly increasing or decreasing rate of 1Hz over a range of 12-50Hz. The diodes are viewed binocularly from one meter and are thus held in foveal fixation. The test requires the subjects to discriminate flicker from fusion and vice versa by pressing the response button held in the preferred hand. Individual thresholds are determined by the psychophysical method of limits (Woodworth & Schlosberg, 1958) as an average response to three ascending (flicker to fusion) and three descending (fusion to flicker) scales presented alternately.

CFF has been shown to correlate closely with other non-performance measures such as EEG measures of arousal (Gortelmeyer & Weinmann 1982, Grunberger et al 1982) and with changes in self reported levels of alertness using visual analogue scales (Grundstrom 1977, Grundstrom 1978; Grandjean et al 1977, Hindmarch et al 1979, Parrott 1982).

The sensitivity of CFF is such that it is able to discriminate and differentiate between different classes of psychoactive compounds, such as sedatives which produce a reduction in CFF threshold and stimulants which cause CNS arousal and consequently elevate the CFF threshold (Smith & Misiak, 1976, Hindmarch 1982).

In addition, CFF can differentiate compounds of the same therapeutic class such as hypnotics (Hindmarch & Fairweather 1994), antidepressants (Hindmarch & Kerr 1994), AHs (Hindmarch & Shamsi 1999), anxiolytics (Hindmarch 1979), and neuroleptics (Hindmarch 1994). CFF is able to detect differences in varying doses of the same drug e.g. temazepam (Hindmarch 1975) and oxazepam (Kerr et al 1992). CFF is also sensitive to subtle changes following the administration of nicotine (Sherwood 1993), tea and coffee (Hindmarch et al 1998) and a range of doses of alcohol (Hindmarch et al 1991, Kerr et al 1991). Kilminster (1991) demonstrated that in a longitudinal study of 3.5
years, no significant regression effects on CFF were observed in a population of healthy elderly volunteers.

Meta-analysis of a series of five studies with a total of 101 subjects, showed the split half reliability of CFF to range from $r = +0.92$ to $r = +0.97$ (Parrott 1982). The test-retest reliability of CFF has been examined by a number of researchers and reported to range between $+0.85$ to $+0.98$ (McNemar 1951, Simonson & Brozek 1952, Agurell et al 1976, Hindmarch 1980, Holmberg 1981, Levander 1982, Parrott 1982).

**Choice Reaction Time (CRT)**

Measurement of reaction time is yet another popular test to be frequently incorporated into psychopharmacological study designs. CRT is used as an indicator of sensorimotor performance, assessing the efficiency of the attentional and response mechanisms in the information processing chain without the need for extended cognitive processing (Hindmarch et al 1988). Many of the everyday skilled activities such as car driving require rapid and yet co-ordinated responses in which the reaction time component is most crucial.

The latency of a motor response to a critical stimulus is recorded, but since this stimulus is one of a number of possible alternatives, attentional monitoring abilities are also measured. The total reaction time (TRT) is regarded as the sum of the two separable components: the stimulus recognition reaction time (RRT) used as measure of attentional monitoring and the motor reaction time (MRT) used as a measure of the efficiency of the response output system.

From a central starting position, using the Leeds Psychomotor Tester (LPT) (Hindmarch 1975) subjects are required to extinguish one of six equidistant red light-emitting diodes, illuminated at random, by touching the appropriate contingent response button. These
light/button combinations are arranged in a 120° arc (24° between each light/button pair) of a 15cm radius circle, centred on and forward of the start button. All buttons are touch sensitive, and there are no switches to engage (Frewer & Hindmarch 1988). Mean reaction times are obtained from the average of 20 consecutive trials. Both recognition (time taken to spot the light and remove the finger from the starting position) and motor (time taken to reach the appropriate response button) components of the total reaction time are recorded automatically.

Measurements of CRT provide information on the constant, very rapid adjustments individuals must make to their environment, which often require them to attend to several potential stimuli at once. This suggests that there is high construct validity inherent in reaction time measures. CRT has been described to be similar to the measurement of brake reaction time (Hindmarch et al 1983).

CRT has been used successfully to assess performance changes following the administration of a wide range of psychoactive compounds, from the barbiturates, which increase reaction times due to their sedative action through to mild cognitive enhancers like methylxanthines, which conversely reduce reaction times (Hindmarch 1990). Similarly, impairments in performance manifested as increases in reaction time have been demonstrated following the administration of first generation AHs (Gaillard et al 1988, Levander et al 1985, Mattila et al 1986). CRT has also been shown to discriminate and differentiate between compounds of the same pharmacological class such as the anxiolytic benzodiazepines (Hindmarch et al 1991). No significant regression effects of CRT were observed in a repeated measures longitudinal study of 3.5 years in healthy elderly volunteers (Kilminster 1991).

A substantial number of studies have been performed with CRT, which show the measure to be valid and reliable. Krause & Bittner (1982) assessed the reliability of a variety of
reaction time tasks and reported that once a performance plateau was reached, test-retest reliability was in excess of $r = +0.58$.

**Sternberg Memory Scanning Task (SMST)**

High speed scanning and retrieval from short term memory was used to investigate the possible effects of AHs on memory using a technique based upon a reaction time method pioneered by Sternberg (1966, 1969). The test involves making simple comparisons of a displayed probe digit against a set of stimuli digits held in short term memory and indicating whether there is or is not a match to the probe in the stimulus set. Typically, subject reaction times are prolonged as the size of the stimulus set increases, suggesting that some internal data comparison takes place before a response is initiated.

When a small stimulus set is used, the memory search task is relatively simple and consequently the final reaction time is dominated by the peripheral processes of perceiving and reacting to the probe. These processes are particularly affected by the level of drug-induced sedation. However, where a larger stimulus set is presented, the reaction time contains greater central memory search and retrieval components, and it is possible to estimate specific effects on memory function.

Subjects are required to memorise a series of one, three or five digits (stimulus set) presented randomly on a visual display unit (VDU). Following the presentation of the stimulus set, an auditory signal is given, which is subsequently followed by a series of single probe digits. Subjects are required to respond to the probe by pressing the “YES” button (positive response) if the probe digit is contained in the stimulus set, or the “NO” button (negative response) if it is not. There are an equal number of positive and negative probe digits in each probe set. Response times are recorded for correct identifications.
The SMST has been shown to be sensitive to the effects of many psychoactive compounds. Subhan & Hindmarch (1984) investigated the amnestic effects of several benzodiazepine hypnotics and reported that the test was able to clearly indicate impairments at both 1 and 10 hours after drug administration. Antidepressants such as amitriptyline and trazadone have also been shown to possess memory impairing effects, effects which are exacerbated when co-administered with alcohol (Hindmarch & Subhan 1986, Kerr et al 1996). Conversely, nootropics such as vinpocetine (Subhan & Hindmarch 1985) and other cognitive enhancers including Ginkgo Biloba extract (Subhan & Hindmarch 1984a) have been shown to improve short term memory retrieval ability.

Carter et al (1980) evaluated the reliability and stability of memory scanning as a performance measure. When used in repeated measures designs, test-retest correlation coefficients in excess of $r = +0.70$ were reported.

**Compensatory Tracking Task (CTT)**

A compensatory tracking task was used to investigate activities inherent in tasks such as car driving which require skilled motor activity in response to complex visual information. CTT assesses the response output mechanisms required for fine motor control, in contrast to the gross motor activity required for CRT.

The advantage of CTT over the many available simple tests is that it requires the subject to divide attention between competing stimuli. Since attentional mechanisms are heavily utilised during tracking, peripheral responses reflect the need for the subject to divide their attention between the tracking and the reaction time task. Simple tests by their very nature, allow the subject to re-allocate cognitive resources and focus on the task in hand,
masking effects which would be salient if the subject was required to undertake additional tasks.

Subjects are required to attend to two tasks. Firstly, to keep a joystick controlled cursor (an equilateral triangle) in line with a target (a similar triangle, but inverted) moving along a horizontal axis in a pseudorandom fashion. Secondly, to respond simultaneously to a visual stimuli presented at random in corners of the screen. Tracking accuracy (RMS) is calculated as the mean deviation from the track program over the trial period with lower scores indicating a more accurate tracking. The mean reaction time (RT) to the peripheral stimuli is also calculated at each presentation.

Compensatory tracking has a high degree of face validity in that it resembles real-world tasks such as vehicle handling (Hindmarch 1988) and target pursuit (Kennedy et al 1981). In a review by Hindmarch (1986), CTT was shown to be as efficient as the on-the-road measures of vehicle manoeuvring and braking in identifying those drugs, which impaired car-driving performance. This suggests that CTT has a high degree of face validity.

As a sensitive measure, CTT can differentiate compounds within the same therapeutic class including antidepressants (Hindmarch et al 1983), hypnotics (Hindmarch & Fairweather 1994) and antihistamines (Hindmarch & Shamsi 1999).

As regards the reliability of CTT, Kennedy et al (1981) calculated a test-retest correlation of $r = +0.78$.

**Wrist Actigraphy (ACT)**

Subjects wear a wrist actigraph (Ambulatory Monitoring Inc. AMA-32C Mini Motionlogger, Ardsley, New York) on their non-dominant wrist for a specific time period according to the requirements of a study. Actigraphy has been shown to be capable of measuring reductions in behavioural activity (sedation) caused by psychoactive
compounds (Stanley 1997, Stanley and Hindmarch 1997). These small wrist watch sized
devices contain a piezoelectric transducer that detects motion and generates a signal
voltage. In zero crossing mode the signal voltage is compared with a reference voltage for
a change in state. The device records the number of changes in state per epoch.
Automatic sleep/wake detection algorithms have been developed and refined until they
now correlate well with traditional sleep EEG in their measurement of sleep time.
al 1992) and these have been incorporated into proprietary ACTION3 software. Data were
down loaded onto an IBM compatible PC. Percentage sleep/wake for the duration of
each visit was scored automatically using the ACTION3 software. Additional analysis of
activity levels required data to be partitioned into larger epochs prior to statistical analysis
using Statistica 4.5 (Stanley 1997). Epoch length was determined by the statistical
software's limitations in the size of ANOVA design (252 variables). Therefore in order to
analyse each entire study period, data was averaged over consecutive 40 minute periods,
whilst for the analysis of the daytime activity (07:30-23:00) a 30 minute period was used.

4.2.2 Visual Analogue Scales (VAS)

In addition to objective measures of performance, subjective reports are also frequently
utilised in demonstrating sedation in studies of psychoactive drugs. Bond and Lader
(1974) developed this measure for the evaluation of the effects of psychoactive drugs on
subjective ratings, although they were originally described in early 1920s (Freyd in 1923,
Hayes & Patterson 1921).

Rating scales usually consist of 100mm horizontal lines in which extreme states of
various feelings are defined at either ends of the line (e.g. happy, not happy). Subjects
are then required to mark the line according to how happy they feel.
Freyd (1923) listed the advantages of the visual analogue scales method over other methods of assessment as being:

1. Simple and easy to explain and to understand.
2. Requires little motivation of the rater.
3. Quick to complete
4. Simple and easy to score.

Amongst other available subjective measures, visual rating scales have been shown to be by far the most accurate, reliable and valid means of obtaining changes in subjective feelings (Aitken 1969). However, despite their common use and listed advantages, self assessments of performance and sleepiness are not as straightforward or reliable as objective measures of sedation. Subjective reports are much more likely to be influenced by transient fluctuations and other factors such as demand characteristics and environmental stimuli than are objective measures of performance. Subjective reports can be unreliable, because by their very nature, sleepiness, somnolence and sedation can impair the self assessment of awareness and thus result in misleading results. In an extensive review by Hindmarch & Shamsi (1999), it was evident that in all studies employing subjective rating scales, conflicting data were reported, and it was therefore concluded that statements about the sedative potential of an antihistamine could not be made solely on data from subjective tests.

Despite the inconsistencies however, if subjective measures are combined with sensitive and reliable objective tests, they can provide useful data.

**Line Analogue Rating Scales for Sedation (LARS)**

The LARS is employed as a measure of the subjective effects of psychoactive drugs. Subjects mark a series of 10 centimetre line analogue scales, indicating their present
feeling with regards to a mid-point, which represents their normal state of mind before treatment began. The mean scores of ratings of 'tiredness', 'drowsiness', and 'alertness', presented among several distracter scales (anxious, happy, relaxed, dizzy, sad, depressed, energetic and clumsy), are taken as a measurement of perceived sedation (Hindmarch & Gudgeon, 1980). The higher the score (in millimetres), the less alert, more tired and drowsy the subject feels. This measure has been shown to correlate well with various objective measures (Parrott 1982) and has been used extensively to detect subjective sedation with many different classes of compounds (Hindmarch & Gudgeon 1980, Hindmarch & Subhan 1986, Hindmarch & Shamsi 1999).

Leeds Sleep Evaluation Questionnaire (LSEQ)

The LSEQ (Hindmarch, 1975, Parrott & Hindmarch 1978, Parrott & Hindmarch 1980) is a visual analogue rating scale designed specifically to enable the reliable assessment of any change of sleep and early morning behaviour following the administration of medications. The test is used to rate subjective impressions of the ease of getting to sleep (GTS), the quality of sleep (QOS), the ease of waking from sleep (AFS) and the coordination of behaviour following waking (BFW).

The LSEQ is completed the morning following the day of drug administration and subjects are required to rate each of the aspects (described above) in relation to their normal state and performance. The LSEQ has been shown to be particularly sensitive to drugs that produce sedation and has been used to differentiate between different drug classes (Parrott & Hindmarch 1980, Hindmarch 1983) as well as to assess sleep promoting properties of various hypnotics (Parrott & Hindmarch 1980).
4.2.3 Various Other Measures of Cognitive and Psychomotor Performance

The following tests were not part of the core test battery, and were added to the test battery in selected experiments only.

Hamilton Anxiety Rating Scale (HAM-A)

Using the HAM-A, an assessment is made during the course of an unstructured interview after which additional information is sought if any specific rating remains unclear. The 14 questions are to some extent somatically biased and cover the whole range of anxiety neurosis. The HAM-A has been extensively used as a measure of change in treatment outcome studies and the overall score is based on both subjective replies and observed behaviour during the interview (Hamilton 1959).

The HAM-A is usually performed in patients by the general practitioner at the beginning and end of a study to measure the level of anxiety at the beginning and end of treatment. A subsequent analysis of the effects of the treatments on both somatic and psychotic subjective-scales of the HAM-A was performed. This scale was included in experiment 7, in which the efficacy of hydroxyzine and lorazepam in alleviating symptoms of anxiety together with its effects on cognitive functioning were investigated.

Cognitive Failures Questionnaire (CFQ)

The CFQ is a measure of self-reported failures in perception, memory and motor function, developed by Broadbent et al (1982). It comprises 25 possible failures covering these three general areas. Subjects rate how often they have experienced each problem during the last four months, using a five point scale (ranging from ‘never’ (0) to ‘very often’ (4)). Scores have been shown to correlate significantly with external ratings of the respondent, for instance, by their spouse, but are not associated
with indices of neuroticism (Broadbent et al., 1982). The CFQ was also incorporated into the design of experiment 7, to allow the investigation of the effects of hydroxyzine and lorazepam on cognitive functioning in patients suffering from generalised anxiety disorder.

**Clinical Global Impression (CGI)**

This physician rated assessment will indicate the global impression of the patient on cognitive functions and sleep. General practitioners were requested to rate their global impression of the patient’s mental functioning and various aspects of sleep (e.g. ease of getting to sleep, quality of sleep, number of awakenings) as very bad, bad, slightly bad, not bad/not good, slightly good, good or very good.

Together with use of psychometric tests and subjective evaluation of the cognitive effects of hydroxyzine in patients within a general practice setting, the CGI was incorporated into the protocol design of experiment 7 to provide a measure of the physician’s impression of the patients as regards their cognitive functioning and sleep following the administration of hydroxyzine and lorazepam.

**Milford Memory Test (MMT)**

The MMT was used as an objective measure of aspects of short term memory and recognition. In the shopping list task, subjects were shown a list of items, which they then recalled immediately. Following this, they were shown the cards from which they chose items appearing in the original list. In the names and faces task, they were shown photographs of named people and were then asked to recall the names when subsequently presented with the photographs only. The MMT can be used in both healthy volunteers
and patient populations. The MMT was included as part of the test battery in experiment 7 to provide an objective measure of the effects of hydroxyzine on memory.

**Digit Span (DS)**

Forward and backward digit span were also performed to assess the immediate effects on short term memory storage. In this test, subjects were asked to repeat a series of digits read to them. Each subject was tested for the retention of digits forward, starting with 4 digits and increasing by 1 after each series (to a maximum of 8 digits) correctly repeated by the subject. Retention of digits in reverse order was also measured. The final score was the sum of the highest series of numbers recalled for both digits forward and reversed (Fudge et al, 1990).

Experiment 7 was designed to investigate the effects of hydroxyzine and lorazepam on various aspects of cognitive functioning including memory. The detrimental effects of the benzodiazepines on various aspects of memory are well documented. The DS was therefore included in the test battery of experiment 7 as an additional memory test to investigate the effects of both hydroxyzine and lorazepam on short term memory storage.

**4.2.4 Peripheral Measures**

**Histamine-Induced Weal and Flare Response (W&F)**

The use of the histamine induced weal and flare test for demonstrating pharmacodynamic activity of histamine receptor antagonists is widely accepted and is the standard validated procedure for the assessment of antihistaminic activity (Cook & Shuster 1980, Malling 1987).

The peripheral H₁ blocking effect of the study drugs was investigated by measuring skin reactivity to histamine before and after drug administration. The skin prick method was
employed using a 10mg/ml histamine solution. A steel lancet with a 1 mm tip and shoulders, thus preventing further penetration of the skin, was pressed at an angle of 90° to the skin surface through a drop of histamine solution. The test was performed on the volar surface of the forearm before and at designated time points after drug intake. Histamine induced weals and flares appearing on the skin were marked with ink after 10 minutes, transferred onto transparencies and measured by a computerised planimetry system.

The histamine induced weal and flare areas were analysed as absolute and as a percent reduction of pre-drug control values. Percent inhibition of the weal and flare was calculated according to the following equation:

\[
\text{Percent suppression} = \frac{\text{W (F) area}_{\text{baseline}} - \text{W (F) area}_t}{\text{W (F) area}_{\text{baseline}}} \times 100
\]

In the evaluation of peripheral effect of AHs, the skin prick method was chosen because it does not induce any artefacts due to the vehicle used for the preparation of the histamine solution.
4.3 Methods

The general study procedures are outlined in this section, although specific study procedures will be further discussed in the following chapter.

4.3.1 General Study Procedures

All studies were performed in accordance with the Declaration of Helsinki (Tokyo and Venice). All studies conformed to the latest GCP/ICH guidelines and were approved by South West Surrey Local Research Ethics Committee and The University of Surrey Ethics Committee. The protocol for experiment seven was also submitted and approved by Cornwall Ethics Committee.

Experiments 1-6 were conducted in healthy volunteers and were single-centre laboratory based studies, carried out at the HPRU. Experiment 7 investigated the use of AHs in patients suffering from Generalised Anxiety Disorder (GAD) in general practice surgeries in the Surrey and Cornwall areas. As the design and purpose of experiment seven is completely different from the other six experiments, the criteria and methods used in this experiment will be discussed separately.

4.3.2 Experiments 1-6 - Healthy Volunteers

Subjects

Subjects, either selected from the extensive HPRU database or recruited through various advertising programmes, who fulfilled the relevant inclusion/exclusion criteria, were entered into the study. All were healthy non-atopic volunteers of either sex, aged between 18-65 years.
The general inclusion/exclusion criteria were as follows:

**Inclusion Criteria**
- Aged between 18-65 years
- Able and willing to give informed consent
- Subject whose General Practitioner consented to their participation

**Exclusion Criteria**
- Concomitant use of psychotropic medication
- Significant history of mental illness, drug allergy, malignancy or chronic drug abuse (including alcohol but excluding nicotine)
- Significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, neurological or haematological disease or abnormality
- Marked laboratory, biochemical or haematological abnormalities considered to be clinically significant by the study physician
- Pregnant or lactating females
- Females of child bearing potential not using adequate contraception
- Current participation in any other clinical study or participation in the previous 90 days
- Any subject that, in the opinion of the investigator was not suitable.

**Informed Consent**
Prior to entering a study, subjects gave their written informed consent. During the consent procedure, adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study were explained by the investigator in the presence of a
witness. It was also clearly explained that the volunteers were completely free to refuse to enter the study or to withdraw from it at any time or that they could be withdrawn from the study if they did not adhere to the instructions. The informed consent procedure was carried out by either the study physician or a suitable qualified person assigned by the physician. Subjects were required to take two copies of the consent form home for consideration and sign one copy and return if they wished to participate in the study. In addition, information sheets clearly describing the study procedures were provided for the subjects.

The subject’s general practitioner was informed and agreement for participation was obtained prior to enrolling a subject onto the study.

Subjects were clearly instructed that participation in the study required them to adhere to all conditions of the study. These required that subjects should not be working overnight nor be engaged in shift work. They were required to go to bed at their usual bedtimes and avoid late nights before a study day. In addition they were instructed to abstain from alcohol, caffeine and nicotine on study days as well as to reduce the intake of these for the duration of the study. Meals were standardised and provided at set times. Subjects were prevented from napping by vigilant members of staff and requested to take part in group activities to prevent boredom.

Medical examination

Following informed consent of the subject and the general practitioner, subjects attended the unit for a medical examination to ensure that they were healthy and satisfied the relevant inclusion/exclusion criteria. During this examination, blood samples were taken for standard biochemical and haematological tests, as well as the measurement of vital signs (blood pressure, heart rate). Urine samples were screened for drugs of abuse and
pregnancy in female volunteers. This procedure was repeated at the end of the study before subjects were signed off a study. In the event of any abnormality whether related to the study drug or not, further tests were carried out until the condition resolved and the laboratory values returned to normal.

Prior to the first study day, subjects were familiarised with study procedures and fully trained on the psychometric test battery in order to preclude any learning effects (Parkin et al. 1987).

4.3.3 Experiment 7 – patient study

Unlike experiments 1-6, experiment 7 was carried out in patients suffering from GAD in general practice.

Subjects

Subjects were patients who presented themselves to their general practitioner. They were male/female patients who fulfilled the following inclusion/exclusion criteria:

**Inclusion Criteria**

- Aged between 18-65 years inclusive
- Able and willing to give informed consent
- Clinical diagnosis of Generalised Anxiety Disorder
- Conformity of the diagnosis according to the criteria in DSM IV.

**Exclusion Criteria**

- Associated major depressive disorder according to DSM IV criteria
• Any treatment with benzodiazepines in the last two months or any other psychoactive
drug in the last month prior to entering the study
• Concomitant psychotropic medication including AHs, which in the opinion of the
investigator would interfere with the study
• Use of propranolol or any other beta blockers and clonidine in the week prior to the
study.
• Patients requiring psychotherapy
• Patients suffering from acute pulmonary insufficiency and airway obstruction.
• Lactation, pregnancy or pregnancy potential (except when actively using effective
means of contraception).
• Known alcohol or drug addiction or abuse
• Known allergy to hydroxyzine or other piperazines, lactose, corn starch or cellulose
• Known allergy to lorazepam, other benzodiazepines, polyethylene glycol, propylene
glycol, or benzyl alcohol
• Known hepatic, renal and cardiac dysfunction and organic cerebral diseases
• Concomitant treatment with scopolamine
• Any subject that in the opinion of the investigator was unsuitable.
Informed Consent

This was obtained as described in the previous section.

Medical Examination

Following the informed consent process, a medical examination was carried out to ensure that the patients were healthy and fulfilled the relevant inclusion/exclusion criteria outlined above. This was repeated at the end of a patient’s participation prior to signing them off the study.

4.4 Experimental Design

All experiments were performed and analysed under double-blind conditions, where neither the subject nor the experimenter was of aware of the given treatment. All treatments were provided in identical forms so that they could not be distinguished from one another. A copy of the treatment code break was held at a secure location at the HPRU in case of an emergency.

Experiments 1-6 were carried out in healthy volunteers and experiment 7 was conducted with patients suffering from Generalised Anxiety Disorder (this experiment will be discussed separately). In all of these studies, treatments were allocated in a random order. In all experiments with the exception of experiment 7, treatments were randomised in a cross-over fashion according to a Latin square, thus each subject acted as their own control and treatment sequences were balanced for carry over effects.

Treatments were separated by a washout period varying from 4-7 days depending on specific study criteria.
Experiment 7 was performed in a population of patients complaining of symptoms of generalised anxiety disorder. Due to the use of patients in this study, several differences were evident in the design when compared to experiments in volunteers. One such difference was that a placebo was not included in this study due to the ethical reasons associated with the use of placebo condition in symptomatic patients. In addition, although the treatments were randomised, the crossover design was not employed and an equal number of patients received either treatment for the duration of the study.

In all studies, adverse events and the use of any concomitant medication was closely monitored and recorded. However as this thesis is concerned only with the psychometric aspects of the second generation AHs, these effects are not discussed in detail. Table 4.1 provides a summary of the study designs.

**Table 4.1: A summary of the experimental design of each study described in this thesis**

<table>
<thead>
<tr>
<th>EXPERIMENTS</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Randomised</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-blind</td>
<td></td>
<td></td>
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<tr>
<td>Cross-over</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verum</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
4.4.1 Statistical Analysis

All data were analysed using analysis of variance techniques (ANOVA). If the ANOVA revealed an overall significant effect, then differences between means were evaluated using post-hoc tests. In the presentation of results (chapter 5), standard statistical notation is used. That is, $F(a,b) = X, p<Y$, where $F$ stands for the F-ratio, $a$ and $b$ are the degrees of freedom associated with the effect and error variance respectively, $X$ is the particular value of $F$, $p$ stands for the probability that the result was due to chance and $Y$ is the particular value of that probability, which was normally set at 0.05 unless otherwise stated (Fairweather 1997).

4.5 Experiments

Each experiment was conducted with a few tests from the core test battery although each study differed from one another in that different tests were employed.

Experiments conducted and described in the thesis are listed in table 4.2.
<table>
<thead>
<tr>
<th>EXPERIMENT</th>
<th>TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A double blind, placebo-controlled, crossover comparison of fexofenadine and loratadine versus placebo: Suppressive effects on histamine-induced weal and flares in healthy volunteers.</td>
</tr>
<tr>
<td>2</td>
<td>A double blind, placebo and verum controlled investigation of the peripheral suppressive effects of fexofenadine, loratadine and promethazone on histamine-induced weal and flare reaction in healthy volunteers.</td>
</tr>
<tr>
<td>3</td>
<td>A double blind, placebo controlled investigation of the effects of fexofenadine, loratadine and promethazine on cognitive and psychomotor function.</td>
</tr>
<tr>
<td>4</td>
<td>An investigation into the effects of cetirizine and loratadine on cognitive function and psychomotor performance in healthy volunteers.</td>
</tr>
<tr>
<td>5</td>
<td>The central effects of three doses of ebastine in healthy volunteers: a double blind, placebo and verum controlled study in healthy volunteers.</td>
</tr>
<tr>
<td>6</td>
<td>The effects of single and repeated administration of ebastine on cognitive and psychomotor performance in comparison to triprolidine and placebo in healthy volunteers</td>
</tr>
<tr>
<td>7</td>
<td>The effects of hydroxyzine and lorazepam on cognitive function and sleep in patients with generalised anxiety disorder.</td>
</tr>
</tbody>
</table>
4.6 Summary

This chapter has outlined the general methods and measures, which have been adopted to evaluate the potency and psychometric profiles of a number of second generation AHs. The test battery has been described, together with information on specific tests and the importance of factors such as reliability and validity has been highlighted. Aspects of subject selection, informed consent, experimental design and statistical analysis have been outlined. Each experiment will be discussed individually and in more detail in the following chapter.
CHAPTER 5: PRESENTATION OF RESULTS

5.0 Chapter Outline

This chapter presents the results of seven experiments, which with the exception of one were all conducted with healthy volunteers. The first part of this chapter presents the results of two experiments, which were designed to investigate the ability of fexofenadine to suppress the histamine-induced weal and flare reaction, which is the standard and validated procedure for the assessment of antihistaminic activity. The second part of this chapter is a presentation of the results of four experiments, designed to assess the cognitive and psychomotor profile of a number of second generation AHs. The third and final section of this chapter presents the results of a study, which was conducted in patients suffering from generalised anxiety disorder within a general practice setting.

For each experiment, all individual tests are presented graphically, however tables of means for all individual data can be found in Appendix I. Results of each experiment are briefly discussed, although a detailed discussion of the findings is presented in chapter six. The general methods and measures employed in each of the experiments have been described in the previous chapter. What follows is a description of specific procedures employed for each experiment.
5.1 Experiment 1: A double-blind, placebo controlled, crossover comparison of fexofenadine and loratadine versus placebo: suppressive effects on histamine-induced weals and flares in healthy volunteers

5.1.1 Introduction & Rationale

Suppression of the histamine induced weal and flare reaction by H₁ receptor antagonists is a commonly used biologic assay for demonstrating the onset and duration of peripheral H₁ blockade (Simons 1996, Simons et al 1990, Simons & Simons 1997, Woodbaker et al 1993) and is the standard validated procedure for the assessment of antihistaminic activity.

The primary objective of this study was to determine the peripheral suppressing effects of fexofenadine in comparison to loratadine, by measuring the attenuation of the histamine induced weal and flare test.

The efficacy of the study drugs were assessed by the following:

1. Speed of onset, defined as the first time a weal size inhibition of ≥35% was observed on day 1.

2. Duration of effect on day 1, assessed as the change from baseline in weal size measurement at 18 and 24 hours.

3. Speed of onset and duration of effect on day 4.

4. Time of maximum inhibition at day 1, defined as the first point when the biggest reduction in weal size measurement from baseline throughout the day.

5. Time of maximum inhibition at day 4.

6. Supportive to the weal measurements, the above were repeated for the flare area measurement.
For statistical purposes, the null hypothesis for the study was that neither fexofenadine nor loratadine would have any effects on the histamine-induced weal and flare test when compared to placebo.

5.1.2 Methods & Measures

The general methods and measures employed in this study are outlined in chapter 4, however the specific procedures are described in the following sections.

Subjects

Eighteen healthy male and female volunteers varying in age from 19-57 years (median age of 34 years) took part in the study. As part of the screening process, each subject was evaluated for skin reactivity to histamine. All subjects completed the study and there were no serious adverse events.

Design

The study was a randomised, double blind, placebo controlled, 3 way crossover study in a group of normal volunteers in which each subject acted as their own control. The treatment sequence was balanced for residual effects using a Latin Square design.

Drugs

The drugs under investigation were fexofenadine 80mg, loratadine 10mg and placebo. Fexofenadine was administered as 40mg twice daily and so a matching capsule was administered with loratadine to preserve the blinding of the study. For the same reason, placebo was also administered twice daily. There was a minimum of 4 days washout period between each treatment cycle. The washout period is calculated on the basis that
the medication will be eliminated from the body in 3.5 half lives. The half-life for fexofenadine is 11-16 hours and it should therefore be largely eliminated from the body during the washout period of 4 days.

Procedure
Following informed consent, medical history and GP approval, all subjects underwent a medical examination. If subjects fulfilled the inclusion / exclusion criteria then they were entered into the study. Each volunteer received active medication or placebo at 08:30 and 20:30. Each treatment was administered for 4 consecutive days with volunteers attending the unit on days 1 and 4. On these assessment days, the subjects stayed overnight at the unit and were tested on the mornings of day 2 and day 5 respectively. On each of the test days, subjects attended the study centre where a breath alcohol reading was taken. Following pre-treatment baseline recordings, treatments were administered and further assessments were performed at 30mins, 45mins, 1hr, 1.5hr, 2hr, 3hr, 4hr, 5hr, 6hr, 8hr, 12hr, 18hr, and 24 hours post dose on days 1 and 4. On days 2 and 3 subjects were required to take their medication at home and subjects were contacted during these days to ensure that the medication had been taken on time.

The use of concomitant medication was discouraged but allowed at the discretion of the physician. The use of alcohol and nicotine were forbidden and products containing caffeine were prohibited on test days. Food consumption was strictly controlled and only allowed at the specified times.
Tests

The peripheral H1 blocking effect of the study drugs were investigated by measuring skin reactivity to histamine using the standard validated weal and flare reaction test, before and at various time points (described above) after drug administration. Weal and flare circumferences were traced at 10 minutes with a felt-tipped pen, transferred onto transparencies and measured by a computerised planimetry system (Seescan Imaging, Seescan Limited, Cambridge).

Assessments of adverse events and concomitant medication were made at each visit.

Statistical Analysis

A two factor analysis of variance was performed with the factors treatment and sequence of drug allocation. Treatment had 3 levels (fexofenadine, loratadine and placebo) and sequence had six levels. Pairwise comparisons between treatment means were analysed using Newman-Keuls tests. Significance was set at p<0.05.

The percentage inhibition was calculated as:

\[
\% \text{ change} = \frac{\text{Weal area baseline} - \text{Weal area at time } t}{\text{Weal area baseline}} \times 100
\]

Baseline weal and flare areas were calculated as the average of the four screening measurements and the two pre-dose measurements.
5.1.3 Results

The mean percentage inhibition of the weal and flare areas on both days 1 and 4, before and up to 24 hours after administration of fexofenadine, loratadine and placebo were calculated and are presented in figures 5.1-5.4. The mean values for both parameters on days 1 and 4 can be found in tables 1-4 of appendix 1.

The two drugs were compared with respect to their ability to suppress the histamine induced weal and flare response, the speed of onset, duration of effect, mean maximum inhibition and the time taken to achieve maximum inhibition.

Suppression of weal and flare by fexofenadine and loratadine versus placebo

Compared to the suppression produced by placebo, fexofenadine significantly suppressed the mean histamine induced weals at 18 and 24 hours on day 1 and at 3 hours on day 4. Fexofenadine also significantly suppressed the formation of flares from 3 to 24 hours on day 1 and from 0.5 to 24 hours on day 4.

Loratadine produced a significant suppression of weals at 4, 6, 8, 18 and 24 hours on day 1, but did not cause any significant suppression on day 4. Flare formation was significantly suppressed at 3, 4, 5, 8, 12 and 24 hours on day 1 following loratadine administration. Significant suppression was evident on day 4 from 0.5 to 24 hours inclusive following the administration of loratadine (figures 5.1-5.4).
Figure 5.1: Percentage inhibition of weal area on day one

Mean values for each treatment

* = p<0.05 when compared to placebo

(Fexo = fexofenadine, Lor = loratadine, o.d. = once daily,
b.d. = twice daily)
Figure 5.2:  Percentage inhibition of weal area on day four
Mean values for each treatment
* = p<0.05 when compared to placebo
(Fexo = fexofenadine, Lor = loratadine, o.d. = once daily, b.d. = twice daily)
Figure 5.3: Percentage inhibition of flare area on day one
Mean values for each treatment
* = p<0.05 when compared to placebo
(Fexo = fexofenadine, Lor = loratadine, o.d. = once daily,
b.d. = twice daily)
Figure 5.4: Percentage inhibition of flare area on day four
Mean values for each treatment
* = p<0.05 when compared to placebo
(Fexo = fexofenadine, Lor = loratadine, o.d. = once daily,
b.d. = twice daily)
**Suppression of weal and flare by fexofenadine and loratadine versus baseline**

Compared to baseline, fexofenadine produced significant suppression of the weals from 2 to 24 hours on day 1 and from 1 to 24 hours inclusive on day 4. Fexofenadine also significantly suppressed flare formation from 1.5 to 24 hours on day 1 and from 0.5 to 8 hours, at 18 and 24 hours on day 4.

Compared to baseline, loratadine produced significant suppression of weal formation from 0.75 to 24 hours on day 1 and from 1 to 4 hours and then from 6 to 24 hours on day 4. Flare formation was significantly suppressed by loratadine on day 1 from 2 to 24 hours inclusive and on day 4 from 0.5 to 24 hours inclusive. Administration of placebo did not result in any significant suppression of either weals or flares (table 5.1).

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>WEAL</th>
<th>FLARE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment ↓</td>
<td>Day 1 time (hrs)</td>
<td>Day 1 time (hrs)</td>
</tr>
<tr>
<td></td>
<td>Day 4 time (hrs)</td>
<td>Day 1 time (hrs)</td>
</tr>
<tr>
<td></td>
<td>Day 4 time (hrs)</td>
<td></td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>2-24</td>
<td>1.5-24</td>
</tr>
<tr>
<td>(40mg b.d.)</td>
<td>1-24</td>
<td></td>
</tr>
<tr>
<td>Loratadine</td>
<td>0.75-24</td>
<td>2-24</td>
</tr>
<tr>
<td>(10mg o.d.)</td>
<td>1-4, 6-24</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = Not significant when compared to baseline
**Speed of onset**

The speed of onset was calculated as the first time an inhibition of ≥ 35% in weal and flare formation was observed. Analysis of the results showed that there was a significant treatment effect as regards weal and flare formation on both days 1 [F (2,24)=3.94, p=0.033] and 4 [F(2,22)= 4.58, p=0.022]. Pairwise comparisons indicated that there were no significant differences between fexofenadine and loratadine, but that both had a significantly faster onset of action than placebo. Mean speed of action as regards weal inhibition was 3.57 hours for fexofenadine on day 1, dropping down to 1.5 hours on day 4. Although not statistically different from loratadine (4.56 hours on day 1 and 1.3 hours on day 4), this was significantly faster than placebo (8.40 hours on day 1 and 5.0 hours on day 4).

Table 5.2 lists the mean speed of onset for all three treatments on both days 1 and 4.

**Table 5.2: Speed of onset in hours (mean ± s.d.) of weal and flare response on days 1 & 4 following the administration of the three treatments**

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>WEAL</th>
<th>FLARE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 4</td>
</tr>
<tr>
<td>Treatment ↓</td>
<td>time (hrs)</td>
<td>time (hrs)</td>
</tr>
<tr>
<td>Fexofenadine (40mg b.d.)</td>
<td>3.57* ± 4.62</td>
<td>1.47* ± 1.30</td>
</tr>
<tr>
<td>Loratadine (10mg o.d.)</td>
<td>4.56* ± 7.60</td>
<td>1.32* ± 0.96</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.40 ± 10.10</td>
<td>5.0 ± 7.65</td>
</tr>
</tbody>
</table>

* = p< 0.05 compared to placebo
**Duration of effect**

In order to calculate the duration of effect, percentage inhibition was calculated at 18 and 24 hours post dose on both days 1 and 4.

At 18 hours post dose, fexofenadine produced 47.2% mean inhibition of the weal area \( (p=0.027) \), dropping down to 38.7% at 24 hours \( (p=0.008) \). Continuous dosing for 4 days resulted in 54.4% inhibition at 18 hours \( (p=0.013) \) and 43.9% inhibition at 24 hours \( (p=0.001) \) with fexofenadine. Loratadine also achieved a similar inhibition of the weal area, although this was not statistically different from fexofenadine. It is evident from the results, that although the two treatments were similar in their duration of action, fexofenadine exhibited a longer duration of effect than placebo.

Analysis of day 1 results as regards % inhibition of the flare area showed a mean duration of action of 81.1% for fexofenadine on day 1, reaching 100% inhibition on day 4. Once again, loratadine appeared to be similar to fexofenadine in its duration of effect, however both treatments had a longer duration of action than placebo.

Table 5.3 lists the % inhibition of the weal and flare response on both days 1 and 4 by all three treatments.
Table 5.3: Mean percentage inhibition of the weal and flare response at 18 & 24 hours post-dose on days 1 & 4

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>WEAL</th>
<th>FLARE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 4</td>
</tr>
<tr>
<td>Treatment</td>
<td>18 hrs</td>
<td>24 hrs</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>47.2* ±22.9</td>
<td>38.7* ±23.4</td>
</tr>
<tr>
<td>Loratadine</td>
<td>44.9* ±23.0</td>
<td>35.8* ±27.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>12.3 ±57.6</td>
<td>8.5 ±60.8</td>
</tr>
</tbody>
</table>

*= p<0.05 compared to placebo

Maximum inhibition & time to maximum inhibition

The mean maximum inhibition achieved by all three treatments was calculated as a percentage of pre-drug control values. In addition the mean time taken to achieve this inhibition was calculated for both weal and flare responses on both days 1 and 4.

As regards mean maximum inhibition of the weal area, analysis of the results demonstrated a significant treatment effect on day 1 [F(2,24)=13.31, p=0.0001] and on day 4 [F(2,22)=12.95, p=0.005] with pairwise comparisons showing the two active treatments not be significantly different from each other but both to be superior to placebo. Significant treatment effects were detected for mean maximum inhibition of flare area on both days 1 [F(2,24)=10.45, p=0.005] and 4 [F(2,22)=9.55, p=0.001], with pairwise comparisons demonstrating the two active treatments to be significantly different from placebo.
Fexofenadine produced a maximum suppression of the weal area of 66% at 12.6 hours, and a maximum suppression of the flare area of 99% at 8.5 hours on day 1. Continuous dosing maintained this inhibition on day 4, with fexofenadine achieving a mean inhibition of 69% at 10.5 hours, and 100% inhibition at 2.1 hours for the weal and flare areas respectively.

Mean maximum inhibition of the weal area as a result of loratadine administration was 62% at 10.1 hours on day 1 and 67% at 10.3 hours on day 4. Loratadine caused a maximum suppression of the flare area of 96% at 7.8 hours on day 1 and 98.5% inhibition at 1.6 hours on day 4.

Although there were no significant differences between the two active treatments, fexofenadine was significantly superior to placebo in achieving maximum inhibition.

Table 5.4 lists the percentage inhibition achieved by all three treatments on both days 1 and 4.

**Table 5.4: Mean maximum inhibition (± s.d.) as a percentage of pre-drug control values for all three treatments**

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>WEAL</th>
<th>FLARE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 4</td>
</tr>
<tr>
<td>Treatment ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fexofenadine (40mg b.d)</td>
<td>66.0* ± 12.40</td>
<td>69.0* ± 10.31</td>
</tr>
<tr>
<td>Loratadine (10mg o.d.)</td>
<td>62.0* ± 16.20</td>
<td>67.0* ± 9.48</td>
</tr>
<tr>
<td>Placebo</td>
<td>46.0 ± 15.45</td>
<td>56.0 ± 11.60</td>
</tr>
</tbody>
</table>

*= p<0.05 compared to placebo
5.1.4 Discussion of Results

In the present clinical study performed under double blind crossover conditions in eighteen healthy subjects, fexofenadine 40mg b.d., a novel H₁ receptor antagonist was compared with loratadine at its recommended dose (10mg o.d.) and placebo. The study was conducted in order to assess the inhibitory effects of both study drugs on the immediate skin reactions induced by histamine and to establish the onset of action as well as the duration of effect of fexofenadine compared to loratadine and placebo.

Significant differences in skin reactivity to histamine were observed between fexofenadine and placebo. The suppressive effects of fexofenadine were significantly more rapid, more pronounced and longer lasting than that of placebo.

Fexofenadine had a mean onset of action of 3.5 hours on day 1, with continuous dosing, reducing it to 1.5 hours on day 4. Suppressive effects were evident up to 24 hours post drug administration on both days 1 and 4 with levels of weal inhibition exceeding 50% on day 4. Flare formation was suppressed to a greater extent, with fexofenadine achieving 100% inhibition at 24 hours on day 4. Maximum inhibition of the weal areas on days 1 and 4 were 66% and 69% respectively following fexofenadine administration. Although significantly superior to placebo in suppressing weal and flare formation, there were no detectable differences between fexofenadine and loratadine. The superiority of fexofenadine over loratadine may have been masked by the administration of the minimum dose of fexofenadine as opposed to loratadine being given at its recommended daily dose.

Previous clinical studies with fexofenadine have shown that 40mg is the lowest effective dose in healthy volunteers (Hoechst Marion Roussel, Personal Communications 1999) and that a dose of 160mg achieved maximum suppression of the histamine-induced weal and flare response (HMR 1999). Subsequent dosing of fexofenadine to 800mg did not
cause further peripheral suppression, but was well tolerated with no increases in
treatment related adverse events (HMR 1999). In a number of seasonal allergic rhinitis
trials, fexofenadine in doses of 40mg to 240mg administered for two weeks was
statistically superior to placebo in reducing SAR symptoms (Bernstein et al 1997).
Results obtained with loratadine in this study are in agreement with previous research in
which loratadine has been shown to possess weak inhibitory effects compared to a
number of other antihistaminics such as cetirizine (Roman et al 1986; Pechadre et al
1991), and similar effects to terfenadine (Gendrau-Reid et al 1986; Kassem et al 1988)
and astemizole (Bateman et al 1986).

From present results, it appears that fexofenadine 40mg b.d is significantly superior to
placebo and as effective as loratadine as regards onset of action, duration of effect and the
ability to suppress the histamine induced weal and flare response.
5.2 Experiment 2: A double blind, placebo and verum controlled investigation of the peripheral suppressive effects of fexofenadine, loratadine and promethazine in healthy volunteers

5.2.1 Introduction & Rationale
In the previous experiment, the suppressive effects of fexofenadine (80mg) and loratadine (10mg) were compared with placebo. Despite the use of a sub-clinical dose of fexofenadine, it was shown to cause significant suppression of the histamine-induced weal and flare reaction when compared to placebo.

As the current recommended clinical dose of fexofenadine is 120mg in the treatment of seasonal allergic rhinitis and 180mg in the treatment of chronic idiopathic urticaria, this study was designed to determine the speed of onset and duration of effect of higher doses of fexofenadine (80mg, 120mg and 180mg) in comparison to loratadine 10mg, promethazine 30mg (as a verum) and placebo in a group of healthy non-atopic volunteers.

For statistical purposes, the null hypothesis for the study was that fexofenadine, loratadine or promethazine would not have any effects on the histamine-induced weal and flare in comparison with placebo.

5.2.2 Methods & Measures

Subjects

Twenty four healthy male and female volunteers, aged 19 to 58 years (mean 32.6 years) participated in this study. As part of the screening procedure, each subject was evaluated for skin reactivity to histamine.
Design

The study was a randomised, double blind, placebo-controlled, 6 way crossover study in a group of non-atopic volunteers, in which each volunteer acted as their own control. The treatment sequence was balanced for residual effects using a Latin square design.

Drugs

The drugs under investigation were fexofenadine 80mg, 120mg and 180mg, loratadine 10mg, promethazine 30mg (as a verum) and placebo. Each treatment day was separated by a washout period of four days or more.

Procedure

Following informed consent, medical history and GP approval, all subjects underwent a medical examination. Subject to fulfilling the inclusion/exclusion criteria, eligible volunteers were entered into the study. Each volunteer received active medication or placebo as a single oral dose at 0830 hours.

On each of the test days, subjects attended the study centre where a breath alcohol reading was taken. Following two pre-treatment baseline recordings (-30mins and 00mins), treatments were administered and further assessments were performed at 30mins, 45mins, 1hr, 1.5hr, 2hr, 3hr, 4hr, 5hr, 6hr, 8hr, 12hr, 18hr, and 24 hours post dose. Weal and flare measurements were made 10 minutes after each skin prick test.

The use of concomitant medication was discouraged but allowed at the discretion of the physician. The use of alcohol, nicotine and products containing caffeine was prohibited on test days. Food consumption was strictly controlled and only allowed at the specified times.

Assessments of adverse events and concomitant medication were made at each visit.
Statistical Analysis

The results for all primary efficacy variables, i.e. speed of onset and duration of effect together with the secondary variable of time of maximum inhibition for both the weal and the flare were all analysed using distribution free methods of analysis. Friedman ANOVA was used to assess overall treatment effects and the Wilcoxon matched pairs to assess pairwise treatment comparisons. The percentage inhibition of the weal and the flare (from baseline) were calculated using the same formula employed in experiment I, in which the baseline was calculated as the average of the four screening measurements and the two pre-dose measurements (-30mins and 00mins).

5.2.3 Results

The mean percentage inhibition of the weal and flare areas, before and up to 24 hours after administration of fexofenadine (80mg, 120mg & 180mg), loratadine (10mg), promethazine (30mg) and placebo were calculated and are presented in figures 5.5 & 5.6. Tables 5.5 and 5.6 present the mean values for both parameters together with the statistical significance obtained at various time points.

The three drugs were compared with respect to their ability to suppress the histamine induced weal and flare response, the speed of onset, duration of effect, mean maximum inhibition and the time taken to achieve maximum inhibition.
Suppression of weal and flare by fexofenadine, loratadine & promethazine versus placebo

Compared to the suppression produced by placebo, fexofenadine administered at all three doses significantly inhibited both the weal and flare reaction at various time points throughout the 24 hour period (tables 5.5 & 5.6). To avoid confusion in the graphs, the significant time points are not indicated on the graph but highlighted in tables 5.5 and 5.6.

The formation of weals were significantly suppressed with fexofenadine 80 mg at 2-5 hours and 8 hours post drug administration (p<0.05). The 120 mg dose of fexofenadine significantly inhibited weal formation from 2-12 hours (inclusive) and the administration of the highest dose of fexofenadine (180 mg) resulted in significant suppression of weal from 1-18 hrs inclusive (p<0.005). Similarly, the 80 mg dose of fexofenadine inhibited flare formation from 2-18 hours post-dose (p<0.005), the 120 mg dose suppressed flare formation from 2-18 hours (p<0.005) and the highest dose of fexofenadine (180 mg) inhibited flare formation from 1.5-24 hours (p<0.005).

Loratadine also produced a significant suppression of both the weal and flare formation, however the inhibitory effects of loratadine were weak when compared to the other treatments. Loratadine significantly suppressed weal formation only at 8 and 12 hours post dose (p<0.005), whereas flare formation was significantly suppressed at 4 hrs and 6-24 hours inclusive following the administration of loratadine (p<0.05). Promethazine suppressed the formation of weals at 1, 2-5, 8 and 12 hours (p<0.05) and similarly the formation of flares at 2-5 and 8-18 hours following drug administration (p<0.05).
Figure 5.5: Percentage inhibition of weal area

Mean values for each treatment

(Fexo = fexofenadine, Lor = loratadine, Prom = promethazine)
Figure 5.6: Percentage inhibition of flare area:

Mean values for each treatment

(Fexo = fexofenadine, Lor. = loratadine, Prom = promethazine)
Table 5.5: Weal Area - percentage change from true baseline and standard deviations (s.d.) for all treatment conditions

(Fexo = fexofenadine, Lor = Loratadine, Prom = promethazine)

<table>
<thead>
<tr>
<th>TIME (HRS)</th>
<th>FEXO 80mg</th>
<th>FEXO 120mg</th>
<th>FEXO 180mg</th>
<th>LOR 10mg</th>
<th>PROM 30mg</th>
<th>PLACEBO</th>
</tr>
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</tbody>
</table>

* = p<0.05 compared to placebo, ** = p< 0.005 compared to placebo
Table 5.6: Flare Area - percentage change from true baseline and standard deviations (s.d.) for all treatment conditions
(Fexo = fexofenadine, Lor = Loratadine, Prom = promethazine)

<table>
<thead>
<tr>
<th>TIME (HRS)</th>
<th>FEXO 80mg</th>
<th>FEXO 120mg</th>
<th>FEXO 180mg</th>
<th>LOR 10mg</th>
<th>PROM 30mg</th>
<th>PLACEBO</th>
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<td>(31.07)</td>
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<td>78.00**</td>
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<td>(25.73)</td>
<td>(37.34)</td>
<td>(285.02)</td>
</tr>
</tbody>
</table>

* = p<0.05 compared to placebo, ** = p<0.005 compared to placebo
Pairwise comparisons between treatments

Pairwise comparisons between the treatments indicated that the effects of fexofenadine were significantly different from loratadine and promethazine at various time points. There were no differences between the two lower doses of fexofenadine as regards the inhibition of either the weal or flare formation, although the highest dose (180mg) was shown to be significantly superior to the former two in inhibiting the histamine-induced weal and flare response. In comparison to loratadine, all three doses of fexofenadine were significantly superior in suppressing the formation of both weals and flares. The effects of fexofenadine occurred in a dose-dependent manner, in which the highest dose (180mg) maintained its superiority over loratadine for a longer period than the other two doses of fexofenadine. The effects of fexofenadine were also significantly different from promethazine as regards the inhibition of both the weal and flare formation at various time points throughout the 24 hour period (tables 5.7).
Table 5.7: Inhibition of weal and flare formation during 24 hours (hrs) - Pairwise comparisons between treatment conditions (p<0.05)

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>COMPARATOR</th>
<th>WEALS (hrs)</th>
<th>FLARES (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine 80mg</td>
<td>Fexofenadine 120mg</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Fexofenadine 180mg</td>
<td>2-3, 5-6, 12</td>
<td>1.5, 3</td>
</tr>
<tr>
<td></td>
<td>Loratadine 10mg</td>
<td>1.5, 3-5, 12 NS</td>
<td>2-4</td>
</tr>
<tr>
<td></td>
<td>Promethazine 30mg</td>
<td>NS</td>
<td>4, 8</td>
</tr>
<tr>
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<td>Fexofenadine 180mg</td>
<td>2, 5-6, 12</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Loratadine 10mg</td>
<td>1.5-5</td>
<td>2-4</td>
</tr>
<tr>
<td></td>
<td>Promethazine 30mg</td>
<td>NS</td>
<td>4, 8</td>
</tr>
<tr>
<td>Fexofenadine 180mg</td>
<td>Loratadine 10mg</td>
<td>1-8</td>
<td>1.5-5, 12</td>
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<tr>
<td></td>
<td>Promethazine 30mg</td>
<td>3-8, 18</td>
<td>2-24</td>
</tr>
<tr>
<td>Loratadine 10mg</td>
<td>Promethazine 30mg</td>
<td>0.5, 1.5-3</td>
<td>2-3</td>
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</tbody>
</table>

NS = Not significant
Suppression of weal and flare by fexofenadine and loratadine versus baseline

Compared to baseline, fexofenadine at all doses produced significant suppression of both the weals and flares from 2 to 24 (p<0.005). However the 180mg dose of fexofenadine significantly inhibited the weal and flare formation at 1.5 hours post dose and significant suppression of the flare was evident with the 120mg dose at 1.5 hours post drug administration (p<0.005).

Compared to baseline, loratadine produced significant suppression of weal formation from 2 to 24 hours (p<0.05) and of the flare formation at 1.5 hours and 3-24 hours post drug administration (p<0.05). Promethazine significantly suppressed the formation of weals from 1-24 hours post dose (p<0.05) and inhibited the formation of flares from 1.5-24 hours post dose (p<0.005). Administration of placebo resulted in significant inhibition of the weal formation at 1.5, 3, and 5-24 hours (p<0.05), as well as inhibition of the flares at 5-8, 18 and 24 hours post-dose (p<0.05) (table 5.8).

Table 5.8: Time in hours (hrs) during which suppression of the histamine induced weals and flares by all treatments was significantly different (p<0.05) from baseline weal and flare areas

<table>
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<tr>
<th>RESPONSE →</th>
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<th>FLARE</th>
</tr>
</thead>
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<tr>
<td>Fexofenadine (80mg)</td>
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<td>2-24 hrs</td>
</tr>
<tr>
<td>Fexofenadine (120mg)</td>
<td>2-24 hrs</td>
<td>1.5-24 hrs</td>
</tr>
<tr>
<td>Fexofenadine (180mg)</td>
<td>1.5-24 hrs</td>
<td>1.5-24 hrs</td>
</tr>
<tr>
<td>Loratadine (10mg)</td>
<td>2-24 hrs</td>
<td>1.5-24 hrs</td>
</tr>
<tr>
<td>Promethazine (30mg)</td>
<td>1-24 hrs</td>
<td>1.5-24 hrs</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.5, 3 &amp; 5-24 hrs</td>
<td>5-8, 18 &amp; 24 hrs</td>
</tr>
</tbody>
</table>
**Speed of onset**

The speed of onset was calculated as the first time an inhibition of ≥ 35% in weal and flare formation was observed. Analysis of the results indicated a significant treatment effect ($X^2 = 28.52$ on 5 d.f., $p<0.001$). Pairwise comparisons showed that fexofenadine 80mg, 120mg, 180mg and promethazine 30mg had a significantly faster onset of action ($p<0.05$) than placebo. In addition, it also revealed that all three doses of fexofenadine were significantly faster than loratadine 10mg. Fexofenadine 180mg was also shown to be significantly faster than the lowest dose of 80mg.

Mean speed of action as regards weal inhibition was 2 hours for fexofenadine 80mg, 1.5 hours for both 120mg and 180mg fexofenadine, 3 hours for loratadine, 1.5 hours for promethazine and 3 hours for placebo (table 5.9). Similarly analysis of the flare results indicated a significant treatment effect ($X^2 = 13.43$, $p<0.020$), with pairwise comparisons revealing that fexofenadine at all dose, loratadine and promethazine were significantly faster than placebo ($p<0.05$).

**Table 5.9:**  Speed of onset in hours (mean ± s.d.) of weal and flare response for all treatment conditions

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>WEAL (hrs)</th>
<th>FLARE (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine 80mg</td>
<td>2 hrs*</td>
<td>1.3 hrs*</td>
</tr>
<tr>
<td>Fexofenadine 120mg</td>
<td>1.5 hrs*</td>
<td>1.3 hrs*</td>
</tr>
<tr>
<td>Fexofenadine 180mg</td>
<td>1.5 hrs*</td>
<td>1.5 hrs*</td>
</tr>
<tr>
<td>Loratadine 10mg</td>
<td>3 hrs</td>
<td>1.8 hrs*</td>
</tr>
<tr>
<td>Promethazine 30mg</td>
<td>1.5 hrs*</td>
<td>1.0 hrs*</td>
</tr>
<tr>
<td>Placebo</td>
<td>3 hrs</td>
<td>3.5 hrs</td>
</tr>
</tbody>
</table>

* = $p<0.05$ compared to placebo
**Duration of effect**

In order to calculate the duration of effect, percentage inhibition of both the weal and the flare were calculated at 18 and 24 hours post dose for all treatments.

As regards the inhibition of the weal, analysis of the results indicated the lack of a significant treatment effects at both 18 hours ($X^2 = 8.52$ on 5 d.f., $p=0.13$) and 24 hours ($X^2 = 3.60$ on 5 d.f., $p=0.61$).

However analysis of the percentage flare inhibition data were indicative of significant treatment effects at both 18 hours ($X^2 = 26.79$ on 5 d.f., $p<0.001$) and 24 hours ($X^2 = 24.58$ on 5 d.f., $p<0.001$). At both time points, fexofenadine at all doses, loratadine 10mg and promethazine 30mg had significantly greater percentage inhibition than placebo (table 5.10).

**Table 5.10:** Mean percentage inhibition of the weal and flare response at 18 & 24 hours post-dose for all treatment conditions

(Fexo = fexofenadine, Lor = loratadine, Prom = promethazine)

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>WEAL</th>
<th>FLARE</th>
</tr>
</thead>
<tbody>
<tr>
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<td>18 hrs</td>
<td>24 hrs</td>
</tr>
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<td>Fexo 80mg</td>
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<td>37.21</td>
</tr>
<tr>
<td>Fexo 120mg</td>
<td>32.68</td>
<td>42.50</td>
</tr>
<tr>
<td>Fexo 180mg</td>
<td>56.25</td>
<td>40.61</td>
</tr>
<tr>
<td>Lor 10mg</td>
<td>43.80</td>
<td>41.63</td>
</tr>
<tr>
<td>Prom 30mg</td>
<td>36.73</td>
<td>34.08</td>
</tr>
<tr>
<td>Placebo</td>
<td>35.58</td>
<td>30.50</td>
</tr>
</tbody>
</table>

* = $p<0.05$ compared to placebo
**Maximum inhibition & time to maximum inhibition**

The mean maximum inhibition achieved by all treatments was calculated as a percentage of pre-drug control values. In addition, the mean time taken to achieve this inhibition was calculated for both the weal and flare responses.

Analysis of the results demonstrated a significant treatment effect for both the mean maximum inhibition of the weal area ($X^2 = 29.39, p<0.000$) as well as the flare area ($X^2 = 33.27, p<0.00001$). Pairwise comparisons revealed significant differences between the three treatments when compared to placebo as well as differences between the three different doses of fexofenadine as regards the maximum inhibition of the weal and flare areas (table 5.11).

**Table 5.11:** Mean maximum inhibition (+ s.d.) of the weal and flare response as a percentage of pre-drug controls with all treatment conditions

(Fexo = fexofenadine, Lor = loratadine, Prom = promethazine)

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>WEAL</th>
<th>FLARE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexo 80mg</td>
<td>74.4*±11.5</td>
<td>98.5*±3.6</td>
</tr>
<tr>
<td>Fexo 120mg</td>
<td>76.3*±8.5</td>
<td>99.4*±1.8</td>
</tr>
<tr>
<td>Fexo 180mg</td>
<td>83.3*±12.7</td>
<td>99.7*±1.0</td>
</tr>
<tr>
<td>Lor 10mg</td>
<td>69.7*±15.1</td>
<td>95.9*±7.2</td>
</tr>
<tr>
<td>Prom 30mg</td>
<td>71.3*±12.2</td>
<td>95.9*±8.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>60.3*±16.5</td>
<td>83.1±26.1</td>
</tr>
</tbody>
</table>

* = $p<0.05$ compared to placebo

† = $p<0.05$ compared to fexofenadine 180mg
As regards time to maximum inhibition of the weal area, analysis of the results demonstrated a significant treatment effect ($X^2 = 16.72$ on 5 d.f., $p<0.005$), with pairwise comparisons showing significant differences between loratadine 10mg and fexofenadine 80mg, 120mg and 180mg. In each case, loratadine had a slower time to maximum inhibition (7 hours) than fexofenadine (5 hours). Fexofenadine 180mg was also significantly faster to maximum inhibition than placebo and promethazine 30mg.

In contrast, analysis of the flare data as regards time to achieve maximum inhibition did not reach significance at the 5% level ($X^2 = 10.98$ on 5 d.f., $p<0.052$).

Table 5.12: Time (hrs) taken to achieve maximum inhibition of both the weal and flare response with all treatment conditions
(Fexo = fexofenadine, Lor = loratadine, Prom = promethazine)

<table>
<thead>
<tr>
<th>RESPONSE →</th>
<th>WEAL  (hrs)</th>
<th>FLARE (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexo 80mg</td>
<td>5 hrs*</td>
<td>5 hrs</td>
</tr>
<tr>
<td>Fexo 120mg</td>
<td>5 hrs*</td>
<td>4 hrs</td>
</tr>
<tr>
<td>Fexo 180mg</td>
<td>5 hrs*+Φ</td>
<td>4.5 hrs</td>
</tr>
<tr>
<td>Lor 10mg</td>
<td>7 hrs</td>
<td>6 hrs</td>
</tr>
<tr>
<td>Prom 30mg</td>
<td>6.5 hrs</td>
<td>5 hrs</td>
</tr>
<tr>
<td>Placebo</td>
<td>6 hrs</td>
<td>5 hrs</td>
</tr>
</tbody>
</table>

*= p<0.05 compared to loratadine
+Φ = p<0.05 compared to placebo and promethazine
5.2.4 Discussion of Results

This experiment was a follow-up of the previous investigation (experiment I), in order to assess the inhibitory effects of higher doses of fexofenadine (120mg and 180mg) on the immediate skin reactions induced by histamine.

Significant differences in skin reactivity to histamine were observed between fexofenadine at all three doses and placebo. The suppressive effect of fexofenadine was significantly more rapid, more pronounced and longer lasting than that of placebo.

The mean onset of action of fexofenadine at the three doses was significantly superior to placebo (fexofenadine 80mg: 2 hrs, 120mg: 1.5 hrs & 180mg: 1.5 hrs). Suppressive effects were evident up to 24 hours post drug administration at all doses of fexofenadine with levels of weal inhibition exceeding 80% with the 180mg. Flare formation was suppressed to a greater extent, with fexofenadine achieving 100% inhibition at 24 hours.

Although significantly superior to placebo in suppressing weal and flare formation, the inhibitory effects of loratadine were weaker when compared to fexofenadine.

Fexofenadine at all doses had a significantly faster onset of action than loratadine (p<0.05). The maximum inhibition of the weal areas achieved with fexofenadine were higher at all doses when compared to loratadine and the time in which this maximum inhibition was achieved was significantly higher with all doses of fexofenadine when compared to loratadine. Findings in this study with loratadine are in agreement with similar investigations in which fexofenadine has been shown to have a significantly faster onset of action than loratadine (Simons & Simons 1997).

Administration of promethazine caused significant suppression of the histamine-induced weal and flare response. However considering that promethazine was administered at three times its recommended dose, the inhibitory effects were weak. This finding is in agreement with previously published literature, in which it has been consistently
demonstrated that high doses of the first generation AHs are required to demonstrate peripheral effects and at these doses, the use of these AHs is associated with excessive CNS side effects (Gendreau-Reid 1986, Simons et al 1986, Simons et al 1990).

From present results, it appears that fexofenadine is significantly superior to placebo and at its dose of 120mg and 180mg significantly superior to loratadine as regards onset of action, and the ability to suppress the histamine induced weal and flare response.
5.3  Experiment 3: A double-blind placebo controlled investigation of the effects of fexofenadine, loratadine and promethazine on cognitive and psychomotor function

5.3.1  Introduction & Rationale

This investigation is the first of a series of experiments designed to assess the cognitive and psychomotor profile of a number of second generation AHs using a battery of sensitive, valid and reliable tests.

In the previous two experiments, the suppressive effects of fexofenadine at doses up to 180mg were compared with loratadine, promethazine and placebo. Fexofenadine was shown to cause significant suppression of the histamine-induced weal and flare reaction when compared to placebo.

The main objectives of this experiment were therefore to assess whether within these doses, fexofenadine has any disruptive effects on aspects of cognitive and psychomotor function in comparison to placebo, loratadine and promethazine, an antihistamine known to produce psychomotor and cognitive impairments.

For statistical purposes, the null hypothesis for the study was that fexofenadine, loratadine or promethazine would not have any effects on cognitive and psychomotor function in comparison to placebo.
5.3.2 Methods & Measures

Subjects

Twenty four healthy male and female volunteers, aged 19 to 58 years (mean 32.6 years) participated in this study. Subjects were required to sleep at the test centre overnight. Subjects were instructed to avoid late nights and to go to bed at their usual bedtime (minimum of 6-8 hours sleep). All subjects completed the study and there were no serious adverse events.

Design

The study was a randomised, double blind, placebo-controlled, 6 way crossover study in a group of healthy volunteers, in which each volunteer acted as their own control. The treatment sequence was balanced for residual effects using a Latin square design.

Drugs

The drugs under investigation were fexofenadine 80mg, 120mg and 180mg, loratadine 10mg, promethazine 30mg (as a verum) and placebo. Each treatment day was separated by a washout period of four days or more.

Procedure

Following informed consent, medical history and GP approval, all subjects underwent a medical examination. Subject to fulfilling the inclusion/exclusion criteria, eligible volunteers were entered into the study. Subjects were familiarised with the study procedures and fully trained on the test battery to preclude any learning effects (Parkin et al 1997). Each volunteer received active medication or placebo as a single oral dose at 0830 hours.
On each of the test days, subjects attended the study centre where a breath alcohol reading was taken. Subjects were then given an actigraph to be worn on the non-dominant wrist for 24 hours. Following pre-treatment baseline recording, treatments were administered and further testing carried out at 1.5, 3, 6, 9, 12 and 24 hours post-dose.

The use of alcohol, nicotine and products containing caffeine were prohibited on test days. Food consumption was strictly controlled and only allowed at the specified times. Subjects were prevented from napping during the day. Assessments of adverse events and concomitant medication were made at each visit.

**Test Battery**

The test battery consisted of Critical Flicker Fusion (CFF), Choice Reaction Time (CRT), Actigraphy (ACT) and Line Analogue Rating Scales for Sedation (LARS). Full description of these tests is provided in chapter 4.

**Statistical Analysis**

The data were analysed as changes from baseline using a 2 factor repeated measures analysis of variance (ANOVA). The factors were treatment (6 levels: fexofenadine 80mg, fexofenadine 120mg, fexofenadine 180mg, promethazine 30mg, loratadine 10mg and placebo) and time (6 levels: 1.5, 3, 6, 9, 12 and 24 hours). *Post hoc* pairwise comparisons between the treatment means were performed using Newman-Keuls tests. All the statistical tests were performed two tailed at the 5% level of significance.
5.3.3 **Results**

**CFF**

Analysis of the changes from baseline showed significant main effects of treatment ($F(5, 85) = 3.51; p < 0.01$) and time of testing ($F(5, 85) = 2.69; p < 0.05$). The results for promethazine 30mg showed a very different pattern from all other treatment regimens, with a marked decrease in the CFF threshold, throughout the 24 hour period, the lowest mean thresholds being from 3-9 hours post medication.

*Post hoc* analysis revealed that overall, promethazine scores were significantly different from placebo, fexofenadine 80mg and loratadine 10mg.

Examination of the results of the drug x interaction showed a consistent reduction in the CFF threshold following the administration of promethazine at 3, 6, 9 and 12 hours when compared to placebo ($p < 0.05$). Promethazine was also significantly ($p < 0.05$) different from fexofenadine 80mg at 3, 6, 9 and 12 hours post medication, from fexofenadine 120mg and loratadine 10mg at 3, 6 and 9 hours and from fexofenadine 180mg at 3 and 9 hours post medication. None of the other treatments could be distinguished from placebo, (figure 5.7).
Figure 5.7: CFF (Hz): Mean change from baseline with all treatments

* = p<0.05 when compared to placebo

(Fexo = Fexofenadine, Lor = Loratadine, Prom = Promethazine)
The results for recognition reaction time (RRT, a component of the total reaction time task), showed no significant main effects of treatment, but there was a significant effect of time ($F(5, 100) = 11.05; p<0.001$) with an increase in reaction time from 1 to 9 hours following the administration of promethazine.

Pairwise comparisons revealed that promethazine 30mg was significantly different from placebo at 3 and 6 hours ($p<0.05$), and from fexofenadine 80mg, 120mg and 180mg and loratadine 10mg at 3 hours, with promethazine having higher mean increases and thus slower reaction times, than the other treatment regimens.

MRT was similar with all drugs.

The results for total reaction time (TRT) showed that there was a significant time effect ($F(5,100)=7.13, p<0.001$) but no significant treatment effect. The post hoc pairwise comparisons did not show any significant differences between the six drugs at any one time point, however the pattern of results show that there was a trend for promethazine to slow reaction times at 3 and 6 hours post dose.
Figure 5.8: RRT: Mean change from baseline for all treatments

* = p<0.05 when compared to placebo

(Fexo = Fexofenadine, Lor = Loratadine, Prom = Promethazine)
LARS

No main effects of drug were evident in the subjective ratings of sedation (LARS), but there were significant effects of time ($F(5, 95) = 5.70; p<0.001$) and the treatment x time interaction was significant ($F(25, 475)=192; p<0.01$). Ratings of sedation were lower with promethazine than with placebo at 12 hours post dose, and this difference was significant at 24 hours post dose ($p<0.05$), (fig. 5.9).

**Figure 5.9:** LARS: Mean change from baseline for all treatments

* = $p<0.05$ when compared to placebo

(Fexo = Fexofenadine, Lor = Loratadine, Prom = Promethazine)
Actigraphy

An analysis of percentage sleep measured by actigraphy revealed a significant increase in the percentage of sleep with promethazine across the study period as compared to all other treatments ($F(5,70)=2.59; p<0.05$). There was a significant increase in the percentage of epochs staged as ‘sleep’ during the day ($F(5,75)=4.46; p<0.002$) with promethazine, however there was no significant difference in the amount of sleep during the night. There was a highly significant main effect of time which, undoubtedly represented the normal circadian and ultradian rhythms.

Figure 5.10: Percent daytime ‘sleep-like’ activity: Mean change from baseline for all treatments

* = $p<0.05$ when compared to placebo

(Fexo = Fexofenadine, Lor = Loratadine, Prom = Promethazine)
5.3.4 Discussion of Results

The present study, which was performed in healthy volunteers under double blind, crossover conditions, was designed to evaluate the central effects of three doses of fexofenadine given as single oral doses.

Fexofenadine, at all three doses tested, was not significantly different from placebo in its effects on psychomotor performance and cognitive function. This is in contrast to the positive control, promethazine, which produced significant impairment of cognitive and psychomotor function as measured by CFF and CRT, for up to 12 hours after drug intake. Loratadine included in this study as a negative internal control and as a comparator, is a non-sedating antihistamine and the present results are in agreement with previous studies (Belaich et al 1990, Mann et al 1989), demonstrating the lack of CNS effects following a 10mg dose of this drug.

These present results are commensurate with the findings of Vermeeren et al (1998), in which they report a lack of CNS effects with fexofenadine at doses up to 240mg on tests of choice reaction time and sustained attention. However, the authors also report an impairment on a critical tracking task with fexofenadine. This observed effect is not consistent, as it appears following single daily doses of 120mg and 240mg but not after a divided dose of 120mg b.i.d.

Vermeeren et al (1998) also claim to have evidence of the activating effects of fexofenadine in that the administration of the higher divided dose reduced the mean SDLP on day 4 compared to placebo and that the combined effects of alcohol and the higher divided dose was significantly less impairing than that of alcohol alone. These present data from our study are contrary to the findings of Vermeeren et al (1998) as CFF thresholds, an objective measure of CNS arousal, show a non significant but dose related trend in the opposite direction to that needed to support notions of intrinsic activation.
Present RRT scores also show no evidence of any dose related activation and thus, speculations regarding the possible activating properties of fexofenadine are not confirmed in this study.

Promethazine, the positive internal control, significantly reduced the CFF threshold by 2.5 Hz up to 9 hours post dose and also increased the recognition reaction time by 40 msec at 3 and 6 hours post dose when compared to placebo. These impairments are greater than those seen with 50mg % of alcohol (Kerr et al 1993) which is the legal limit of alcohol in many countries.

Promethazine has previously been shown to cause a reduction in daytime behavioural activity for up to six hours post dose (Stanley et al 1997). Periods of very low behavioural activity are scored as sleep by the ACTION3 algorithm, so a reduction in activity is mirrored in an increase in ‘sleep like’ behaviour. In this, and our previous study (Stanley et al 1997), we have demonstrated that reduced behavioural activity, here expressed as an increase in daytime ‘sleep like’ behaviour, is reflected as a reduction in psychomotor performance and can thus be regarded as a measure of sedation.

There were no subjective reports of sedation as measured by LARS with any of the treatments including promethazine. Ratings of sedation were lower with promethazine than with placebo at 24 hours post dose and given the overall pattern of results, this is likely to be a type I error.

It is of concern that a 30mg dose of promethazine, reduced the CFF threshold by 2.5Hz up to 12 hours post dose and yet subjects reported themselves as being mentally alert throughout the 24 hour test period. This implies that although subjects feel alert, they are objectively compromised as far as their ability to process information is concerned. Such discrepancies have important implications for the use of AHs in practice where patients are warned not to operate machinery or drive if they feel sedated (Hindmarch 1999).
The aim of this study was to investigate the effects of fexofenadine on a widely validated test battery known to be sensitive to the effects of psychoactive drugs on cognitive and psychomotor performance. The general conclusion that can be drawn from the present study is that there were no subjective or objective effects on psychomotor performance following the administration of fexofenadine and thus allow the conclusion that fexofenadine at doses up to 180mg is free from disruptive effects on the central nervous system.
5.4 Experiment 4: An investigation into the effects of cetirizine and loratadine on cognitive function and psychomotor performance in healthy volunteers

5.4.1 Introduction & Rationale

In the previous experiment, the cognitive and psychomotor effects of various doses of fexofenadine were compared to loratadine, promethazine and placebo in a group of healthy volunteers. In order to extend our investigation into the effects of other second generation AHs, the effects of various doses of cetirizine were compared with loratadine, promethazine (as a verum) and placebo.

The main objectives of this experiment were to determine if in healthy non-atopic volunteers, cetirizine (2.5mg, 5mg & 10mg) has any impact on cognitive and psychomotor function and how the psychomotor profile of cetirizine compares to that of loratadine, promethazine and placebo.

For statistical purposes, the null hypothesis for the study was that cetirizine, loratadine or promethazine would not have any effects on psychomotor function as assessed by a battery of valid, sensitive and reliable tests, in comparison to placebo.

5.4.2 Methods & Measures

Subjects

Twenty four healthy non-atopic volunteers (16 female, 8 male) aged between 18 and 58 years (mean age of 34.7yrs) participated in this study. Subjects were instructed to avoid late-nights and to go to bed at their usual bedtime (minimum of 6-8 hours sleep). All subjects completed the study and there were no serious adverse events.
Design

The study was a randomised, double blind, placebo-controlled, 8 way crossover study in a group of healthy volunteers, in which each volunteer acted as their own control. The treatment sequence was balanced for residual effects using a Latin square design.

Drugs

The drugs under investigation were cetirizine 2.5mg, 5mg & 10mg, loratadine 10mg, 20mg & 40mg, promethazine 25mg (as a verum) and placebo. Each treatment day was separated by a washout period of six days or more.

Procedure

Following informed consent, medical history and GP approval, all subjects underwent a medical examination. Subject to fulfilling the inclusion/exclusion criteria, eligible volunteers were entered into the study. Subjects were familiarised with the study procedures and fully trained on the test battery to preclude any learning effects (Parkin et al 1997). Each volunteer received active medication or placebo as a single oral dose at 0900 hours.

On each of the test days, subjects attended the study centre where a breath alcohol reading was taken. Pre-treatment baseline recordings were made on each of the psychometrics (described below) after which medications were administered and further testing carried out at 1.5, 3 and 6 hours post-dose.

The use of alcohol and nicotine were forbidden and products containing caffeine were prohibited on test days. Food consumption was strictly controlled and only allowed at the specified times.

Assessments of adverse events and concomitant medication were made at each visit.
**Test Battery**

The test battery consisted of Critical Flicker Fusion (CFF), Choice Reaction Time (CRT), Compensatory Tracking Task (CTT) and Line Analogue Rating Scales for Sedation (LARS).

**Statistical Analysis**

The data were analysed as changes from baseline using a 2 way repeated measures analysis of variance (ANOVA). The factors were treatment (8 levels: cetirizine 2.5mg, 5mg & 10mg, loratadine 10mg, 20mg, 40mg, promethazine 25mg & placebo) and time (3 levels: 1.5, 3 and 6 hours). *Post hoc* pairwise comparisons between the treatment means were performed using Newman-Keuls tests. All the statistical tests were performed two tailed at the 5% level of significance.

**5.4.3 Results**

The mean response data are presented in tables 11-13 of Appendix 1.

**CFF**

Analysis of the results showed a significant treatment effect ($F(7,161)=2.309, p<0.029$) and a highly significant time effect ($F(2,46)= 14.186, p<0.001$), although the treatment x time interaction was not significant. Pairwise comparisons, using Newman-Keuls, between treatment means showed that promethazine 25 mg was significantly ($p<0.05$) different from cetirizine 2.5mg, cetirizine 10mg, loratadine 10mg and loratadine 40mg, there being a significantly greater reduction in CFF on promethazine. The other comparisons did not reach significance at the 5% level ($p=0.07$ for placebo & cetirizine 5mg; $p=0.069$ for loratadine 20mg). Examination of the treatment comparisons at each
time point showed that promethazine 25mg had a significantly greater reduction than all other treatments at 3 and 6 hours post dose, (fig 5.11).

Figure 5.11: Critical Flicker Fusion (Hz): Mean change from baseline for all treatments

* = p<0.05 when compared to placebo

+ = p<0.05 when compared cetirizine & loratadine at all doses

(Cet = Cetirizine, Lor = Loratadine, Prom = Promethazine)
CRT

Analysis of the total reaction time (TRT) component of the CRT task revealed a significant treatment effect \[F(7,119)=3.21, p=0.003\]. Pairwise comparisons, using Newman Keuls, between treatment means showed that promethazine was significantly different from placebo, cetirizine 2.5 and 10 mg, and loratadine 10 and 20 mg at three hours post drug administration, (figure 5.12). This analysis was based on 18 subjects with complete data as a few problems were encountered with the test equipment, which consequently led to some data loss.

Analysis of the results for the recognition reaction time component of the CRT task failed to reach significance at the 5% level \[F(7,119)=1.99, p=0.061\], although at 3 hours post drug administration results were suggestive of a main treatment effect with loratadine 20 & 40 mg causing large increases in reaction time, a result also reflected in the total reaction time means.

There were no significant differences on motor reaction time component between any of the treatments.
Figure 5.12: Total Reaction Time (msec): 3 hours post-dose with all treatments

* = p<0.05 when compared to placebo
+

(Cet = Cetirizine, Lor = Loratadine, Prom = Promethazine)
For CTT, analysis of the results showed that there were no significant treatment, time or treatment x time interaction on either tracking error or peripheral reaction time.

The average of the two scores for ‘tired’ and ‘drowsy’ of the LARS was used to given an overall score of subjective sedation. Analysis of the results showed a significant treatment effect \([F(7,161)= 3.530, p=0.001]\) but no significant time or treatment x time interaction. Pairwise comparisons, using Newman Keuls, between treatment means showed that promethazine 25 mg was significantly \((p<0.05)\) different from all the other seven treatments, there being a greater increase in sedation with promethazine. Neither of the three doses of cetirizine nor loratadine were associated with subjective reports of sedation at any point throughout the day. Promethazine caused significantly greater increase in subjective reports of sedation when compared to placebo at all time points \((p<0.05)\), (figure 5.13).
Figure 5.13: Line Analogue Rating Scales for Sedation (mm): Mean change from baseline for all treatments

* = p<0.05 when compared to placebo

(Cet = Cetirizine, Lor = Loratadine, Prom = Promethazine)
5.4.4 Discussion of Results

Cetirizine, at all three doses tested, was not significantly different from placebo in its effects on psychomotor performance and cognitive function. This is in contrast to the positive control, promethazine, which produced significant impairment of cognitive and psychomotor function as measured by CFF, CRT and LARS, for up to 6 hours after drug intake. Promethazine, the positive internal control, significantly reduced the CFF threshold by 2.30Hz up to 6 hours post dose when compared to placebo.

These present results are commensurate with previous published literature in which cetirizine has been shown to be free of CNS adverse effects at doses up to 20 mg (Schweitzer et al 1994, Tharion et al 1994, Simons et al 1995, Simons et al 1996). At therapeutic doses (5-20 mg), cetirizine did not produce daytime sedation, as indicated by its lack of effect in the MSLT (Seidel et al 1987, Seidel et al 1990). Cetirizine did not cause any significant impairment of psychomotor performance, as assessed by CFF, simple reaction time, finger tapping and Stroop word tests (Gengo et al 1987). In 36 healthy volunteers included in a placebo-controlled double-blind cross-over trial, cetirizine 10mg did not significantly affect psychomotor performance as assessed by 5 objective psychometric tests or subjective assessments of mood and health, and the concomitant administration of cetirizine 10mg and alcohol did not significantly potentiate the impairment occurring after alcohol alone (Doms et al 1988).

A number of studies have also reported subjective and objective evidence of sedation with high doses of cetirizine and evidence exists to support the notion that cetirizine does possess sedative activity when it is administered at doses higher than those recommended by the manufacturer (Gengo & Gabos 1987, Riedel et al 1990a).

Loratadine included in this study as a comparator, is a non-sedating antihistamine and the present results are in agreement with previous research demonstrating a general lack of
detrimental CNS effects following a 10 mg dose of this drug (Bradley & Nicholson 1987, Roth et al 1987).

Administration of higher doses of loratadine has been reported to cause sedation (Bradley & Nicholson 1987, O’Hanlon 1988, Riedel et al 1990b, Roth et al 1987) and the results from this study support these findings. Following the administration of the 40mg dose of loratadine in this study, impairments were noted on the total reaction time component of the CRT task at 3 hours after drug intake. The increase in reaction time with loratadine at its highest dose closely resembled the impairments evident with promethazine, although it failed to reach statistical significance at the 5% level.

A review of the effects of loratadine at doses ranging from 10-40 mg, on cognitive function and psychomotor performance (Hindmarch & Shamsi 1999), clearly demonstrated that loratadine was free of CNS adverse effects when administered at its recommended therapeutic dose of 10 mg daily. However when the dose was increased, reports of sedation measured both objectively and subjectively increased accordingly. As a whole, loratadine was investigated in 8 studies in which 16 different psychometrics were used. Impairments were found with 11 of which 8 were associated with the 20 and 40mg dose.

It would therefore appear that loratadine at doses above that recommended by the manufacturer, does influence psychomotor function in the CNS even if this action is difficult to discern. What the tests show in this trial as well as those observed in other published studies is that some blood-brain barrier passage is occurring with loratadine. While the doses which appear to be causing the sedation are higher than those recommended by the manufacturer, a powerful reduction in the histamine induced weal and flare response is only achieved with a 40mg dose of loratadine which in terms of
antihistaminic efficacy has been shown to correspond to a 10 mg dose of cetirizine (Rihoux 1990).

The present study, which was performed in 24 healthy volunteers under double blind, crossover conditions, was aimed at evaluating and comparing the central effects of three doses of cetirizine with three doses of loratadine given as single oral doses. A positive control was included in the study to ensure the validity of the methods employed. The choice of the doses was based on previous clinical pharmacological studies, which have shown cetirizine 10 mg to be a more potent inhibitor of histamine induced skin reactions than loratadine 10 mg (Rihoux et al 1990).

The subjective evaluation of the central effects did not show any significant modification with either cetirizine or loratadine when compared with placebo. With respect to the objective measures, all the measurements were unchanged after cetirizine intake irrespective of the dose and time after administration, a result that is in agreement with previous studies. In addition, there were no significant modifications in the objective tests following the administration of the lower doses of loratadine.

The general conclusion that can be drawn from the present study is that there were no subjective or objective effects on psychomotor performance following the administration of cetirizine. This is in contrast to the effects of older, traditional AHs on various tests of psychomotor and cognitive function (Alford et al 1989, Clarke & Nicholson 1978, Cohen et al 1985, Gengo et al 1987, Hindmarch & Shamsi 1999, Seidel et al 1987).

Findings from this study allow the conclusion that cetirizine at its recommended daily dose of 10 mg is free from disruptive effects on the CNS and should therefore prove valuable in the treatment of various allergic disorders in patients who wish to continue with their everyday activities without experiencing decrements in their psychomotor and cognitive abilities.
5.5  Experiment 5: The central effects of three doses of ebastine: a double blind placebo and verum controlled study in healthy volunteers

5.5.1  Introduction & Rationale
Further to the investigation of the effects of fexofenadine, loratadine and cetirizine on cognitive and psychomotor function, this study was undertaken to assess the CNS profile of various doses of yet another second-generation antihistamine in healthy volunteers.

Ebastine is a selective and long acting H1 receptor antagonist, which penetrates the brain poorly, thus allowing an effective blockade of peripheral H1 receptors without CNS side effects when administered within its ‘dose window’ (Wiseman & Faulds 1996).

This study was therefore designed to determine if in healthy non-atopic volunteers, ebastine (10mg, 20mg & 40mg) has any impact on cognitive and psychomotor function and how the psychomotor profile of ebastine compares to that terfenadine, triprolidine (as a verum) and placebo.

For statistical purposes, the null hypothesis for the study was that ebastine, terfenadine, or triprolidine would not have any effects on psychomotor function as assessed by a battery of valid, sensitive and reliable tests, in comparison to placebo.

5.5.2  Methods & Measures
Subjects

Twelve healthy non-atopic volunteers (6 female, 6 male) aged between 18 and 55 years (mean age of 36.2yrs) participated in this study. Subjects were instructed to avoid late-nights and to go to bed at their usual bedtime (minimum of 6-8 hours sleep). All subjects completed the study and there were no serious adverse events.
Design

The study was a randomised, double blind, placebo-controlled, 6 way crossover study in a group of healthy volunteers, in which each volunteer acted as their own control. The treatment sequence was balanced for residual effects using a Latin square design.

Drugs

The drugs under investigation were ebastine 10mg, 20mg & 40mg, terfenadine 60mg, tripolidine 5mg (as a verum) and placebo. Each treatment day was separated by a washout period of seven days or more.

Procedure

Following informed consent, medical history and GP approval, all subjects underwent a medical examination. Subject to fulfilling the inclusion/exclusion criteria, eligible volunteers were entered into the study. Subjects were familiarised with the study procedures and fully trained on the test battery to preclude any learning effects (Parkin et al 1997). Each volunteer received active medication or placebo as a single oral dose at 0900 hours.

On each of the test days, subjects attended the study centre where a breath alcohol reading was taken. Pre-treatment baseline recordings were made on each of the psychometrics (described below) after which medications were administered and further testing carried out at 1.5, 3.5 and 6.5 hours post-dose. In addition to these testing times, a number of tests (CFF, CRT & LARS) were also performed at 0.5 hours post drug administration.

The use of concomitant medication was discouraged but allowed at the discretion of the physician. The use of alcohol and nicotine were forbidden and products containing
caffeine were prohibited on test days. Food consumption was strictly controlled and only
allowed at the specified times.
Assessments of adverse events and concomitant medication were made at each visit.

**Test Battery**
The test battery consisted of Critical Flicker Fusion (CFF), Choice Reaction Time (CRT),
Compensatory Tracking Task (CTT), Sternberg Memory Scanning Task (SMST), and
Line Analogue Rating Scales for Sedation (LARS).

**Statistical Analysis**
The data were analysed as changes from baseline using a 2 way repeated measures
analysis of variance (ANOVA). The factors were treatment (6 levels: ebastine 10mg,
20mg & 40mg, terfenadine 60mg, triprolidine 5mg & placebo) and time (4 levels: 0.5,
1.5, 3.5 and 6.5 hours). *Post hoc* pairwise comparisons between the treatment means
were performed using Newman-Keuls tests. All the statistical tests were performed two
tailed at the 5% level of significance.

**5.5.3 Results**
The mean response data are presented in tables 14-19 of Appendix 1.

**CFF**
Analysis of the results showed a significant treatment effect ($F(5,85)=3.51$, $p<0.01$).
Pairwise comparisons, using Newman-Keuls, between treatment means showed that
triprolidine 5 mg was significantly ($p<0.05$) different to placebo at 1.5 hours post drug
administration. Triprolidine was also shown to cause significant decrements in the CFF
thresholds at 1.5 and 3.5 hours post-dose when compared to its own baseline ($p<0.05$).
CFF scores were not affected with any dose of ebastine or terfenadine at any point during the day (figure 5.14).

**Figure 5.14:** Critical Flicker Fusion (Hz) – Mean change from baseline following the administration of ebastine, terfenadine, triprolidine and placebo

* = \( p < 0.05 \) when compared to placebo

+ = \( p < 0.05 \) when compared to baseline
**CRT**

Analysis of the total reaction time (TRT) component of the CRT task revealed no treatment related effects. However, significant treatment effect

\[ F(5,85) = 3.21, p < 0.01 \]

were evident with the recognition reaction time component of the CRT.

Pairwise comparisons, using Newman Keuls, between treatment means showed that ebastine 10mg caused a significant increase in recognition reaction time at 1.5 hours post-dose \( p < 0.05 \) in comparison to placebo (figure 5.15).

Compared to baseline, ebastine 20mg caused a significant increase in recognition reaction time at 6.5 hours. Increasing the dose of ebastine to 40mg resulted in a dose related increase in RRT at 3.5 and 6.5 hours post-dose when compared to baseline.

There were no significant differences in the motor reaction time component of the CRT between any of the treatments.

Although the TRT results failed to achieve statistical significance at the 5% level \( F(5,87) = 1.99, p = 0.061 \), results were suggestive of a main treatment effect with ebastine 40mg causing large increases in reaction time, a result also reflected in the total reaction time means (figure 5.16).
Figure 5.15: Recognition Reaction Time (msec) – Mean changes from baseline following the administration of ebastine, terfenadine, triprolidine and placebo

* = p<0.05 when compared to placebo

+ = p<0.05 when compared to baseline
Figure 5.16: Total Reaction Time (msec): Mean change from baseline following the administration of ebastine, terfenadine, triprolidine and placebo.
Analysis of the results demonstrated significant treatment effects for both the peripheral reaction time (RT) and the tracking accuracy measure. Triprolidine showed a statistically significant increase in reaction time at 1.5 hours post-dose when compared to placebo (figure 5.17). Similarly, the highest dose of ebastine (40mg) also resulted in significant increases in reaction time at 1.5 and 6.5 hours post-dose.

When compared to baseline, ebastine 20mg increased the reaction time at 6.5 hours post-dose (p<0.05). The administration of terfenadine did not affect either the reaction time or the tracking accuracy at any time point during the day.

The tracking accuracy was not affected by triprolidine or terfenadine. However, compared to placebo, the highest dose of ebastine (40mg) was shown to significantly impair tracking accuracy at 1.5 and 6.5 hours post drug administration (figure 5.18). The impairment caused by the 40mg ebastine was also significantly greater than its baseline at 1.5 hours post-dose (p<0.05).

The lower doses of ebastine did not demonstrate any effects on this parameter.
Figure 5.17: Critical Tracking Task- Reaction time (msec)

Mean change from baseline for all treatments

* = $p<0.05$ when compared to placebo

+ = $p<0.05$ when compared to baseline

![Graph showing mean change from baseline for all treatments with different treatments indicated.](image-url)
Figure 5.18: Critical Tracking Task – Tracking Accuracy

Mean change from baseline for all treatments

* = p<0.05 when compared to placebo

+ = p<0.05 when compared to baseline
The average of the three scores for ‘tired’, ‘drowsy’ and ‘alert’ of the LARS was used to given an overall score of subjective sedation. Analysis of the results showed a significant treatment effect with pairwise comparisons demonstrating that triprolidine significantly increased the subjective reports of sedation at 1.5 hours post drug administration when compared to placebo (p<0.05). Subjective reports of sedation were not affected with any of the three doses of ebastine or terfenadine at any point throughout the day (figure 5.19).

Figure 5.19: Line Analogue Rating Scales for Sedation (mm) – Mean change from baseline for all treatments

* = p<0.05 when compared to placebo
5.5.4 Discussion of Results

The investigation of the effects of ebastine at doses up to 40mg revealed interesting results.

While completely free of CNS impairing effects at the 10mg dose, ebastine caused significant impairment of cognitive and psychomotor function when the doses were increased. The detrimental effects produced by the higher dose of ebastine were very similar to results obtained with the positive control, triprolidine.

Triprolidine produced significant impairment of cognitive and psychomotor function as measured by CFF, CRT, SCTT and LARS for up to 6.5 hours after drug intake.

Terfenadine, a second-generation non-seating antihistamine, was included in the study design as a comparator. Findings with terfenadine are in agreement with previous literature, in which it has been demonstrated that terfenadine is free of CNS adverse effects when the dose is not excessively increased (Gaillard et al 1988, Kerr et al 1993, Tharion et al 1994, Witek et al 1995).

With regards to the findings with ebastine, these present results are commensurate with previous published literature in which ebastine has been shown to be free of CNS adverse effects at doses up to 20mg (Azcona et al 1992, Brookhuis et al 1993, Hopes et al 1992, Mattila et al 1992, Vincent et al 1988a). However at doses above the therapeutic range (50-90 mg), ebastine has been shown to cause sedation and impairment of performance (Vincent et al 1988a, Barbanoj 1988). The drug is clearly not sedative within its ‘dose window’, however it appears to be capable, at higher doses, of inducing a decrement in performance. This is evidenced by the increase in reaction time component of the CRT together with increases in reaction time component of the tracking test as well as reducing tracking accuracy.
It is also evident that the CNS impairing effects were still present at 6.5 hours post-dose. This has important implications for the use of ebastine as it has been shown that the maximal anti-histaminic action of ebastine occurs between 8 to 12 hours post-dose (Wiseman & Faulds 1996).

The present study, which was performed in 12 healthy volunteers under double-blind, crossover conditions, was aimed at evaluating and comparing the central effects of three doses of ebastine with tripolidine, a sedative antihistamine known to produce cognitive and psychomotor impairments (Betts et al 1984, Brookhuis et al 1993, Riedel et al 1990a).

Although this study only uses twelve subjects, the power was sufficient to show tripolidine acting as a positive internal control and ebastine having an effect on various tests of cognitive and psychomotor performance.

Given the importance of using AHs that are without unwanted CNS effects, a follow-up experiment (experiment 6) was designed to investigate the effects of repeated dosing of ebastine on various aspects of cognitive and psychomotor function.
5.6 Experiment 6: The effects of single and repeated administration of ebastine on cognition and psychomotor performance in comparison to triprolidine and placebo in healthy volunteers

5.6.1 Introduction & Rationale

The investigation of the central effects of single doses of ebastine in the previous experiment clearly showed that at higher doses (40mg), ebastine is associated with significant impairments of cognitive and psychomotor functioning. This experiment was therefore designed to investigate the effects of repeated doses of ebastine (10-30mg) on various aspects of cognitive and psychomotor performance in healthy volunteers. Triprolidine 10mg (sustained release formulation) was included in the study as positive internal control.

For statistical purposes, the null hypothesis 'for the study was that neither ebastine, nor triprolidine would have any effects on cognitive and psychomotor function as assessed by a battery of valid, sensitive and reliable tests, in comparison to placebo.

5.6.2 Methods & Measures

Subjects

Ten healthy non-atopic female volunteers aged between 22 and 39 years (mean age of 27.3yrs) participated in this study. Subjects were requested to avoid late-nights and refrain from consuming alcohol the night before each study period.

All subjects completed the study and there were no serious adverse events.
Design
The study was a randomised, double blind, placebo-controlled, 5 way crossover, repeated dosing study in a group of healthy volunteers, in which each volunteer acted as their own control. The treatment sequence was balanced for residual effects using a Latin square design. Each treatment period comprised of five days in which testing was performed on days 1 and 5.

Drugs
The drugs under investigation were ebastine 10mg, 20mg & 30mg, triprolidine 10mg (sustained release formulation as a verum) and placebo. Each treatment day was separated by a washout period of seven days or more.

Procedure
Following informed consent, medical history and GP approval, all subjects underwent a medical examination. Subject to fulfilling the inclusion/exclusion criteria, eligible volunteers were entered into the study. Subjects were familiarised with the study procedures and fully trained on the test battery to preclude any learning effects (Parkin et al 1997).

On each of the test days, subjects attended the study centre where a breath alcohol reading was taken. Each test day began with pre-treatment baseline assessments on the psychometric (described below) after which the first treatment dose was administered. Performance using a full test battery was assessed at 2, 4, and 8 hours after drug administration on day 1, (D1H2, H4 & H8). In addition to these testing times, a number of tests (CFF, CRT & LARS) were also performed at one hour post drug administration (D1H1).
On day 5, the same tests were performed before the administration of the treatments (D5H0) and at the same time intervals thereafter (D5H1, H2, H4 & H8). A Leeds Sleep Evaluation Questionnaire (LSEQ) was completed on the morning of day 1 (D1H0), 2 (D2H0) and 6 (D6H0). Medication was administered under supervision at the same time on days 2, 3 and 4.

Reports of all adverse events and use of concomitant medication were recorded at each visit. Caffeine, nicotine and alcohol were forbidden on study days. Subjects were prevented from napping during the day by members of staff and were encouraged to keep themselves occupied by engaging in group activities.

Test Battery

The test battery consisted of Critical Flicker Fusion (CFF), Choice Reaction Time (CRT), Compensatory Tracking Task (CTT), Sternberg Memory Scanning Task (SMST), Line Analogue Rating Scales for Sedation (LARS) and the Leeds Sleep Evaluation Questionnaire (LSEQ).

Statistical Analysis

The data were analysed as changes from baseline using a three way repeated measures analysis of variance (ANOVA). The factors were treatment (5 levels: ebastine 10mg, 20mg & 30mg, triprolidine 10mg & placebo, time (4 levels: 1, 2, 4 and 8 hours) and day (2 levels: 1 & 5). Post hoc pairwise comparisons between the treatment means were performed using 2 tailed 95% confidence intervals. All the statistical tests were performed two tailed at the 5% level of significance.

The assumption of normality of data was examined by probability plots and found to be acceptable.
5.6.3 Results

The mean response data are presented in tables 20-27 of Appendix 1.

CFF

Analysis of results did not reveal any significant placebo versus treatment differences on either day 1 or 5. However, a decrement in CFF threshold was seen with all treatments on both days, reflecting a general lowering of alertness during the course of the day (figure 5.20).

Figure 5.20: Critical Flicker Fusion (Hz) – Mean change from baseline (H0) on day 1 following the administration of ebastine, triprolidine and placebo

(Eba = Ebastine, Tri = Triprolidine)
Figure 5.21: CFF (Hz): Mean change from baseline (D1H0) on day 5 following the administration of ebastine, tripolidine and placebo

(Eba = Ebastine, Tri = Tripolidine)
**CRT**

Analysis of the CRT results did not demonstrate any significant treatment, time or treatment x time interaction on either the recognition, motor or total reaction time. These findings were not even suggestive of a particular trend and are therefore not discussed further.

**CTT**

Analysis of the reaction time (RT) component of the SCTT revealed a significant treatment effect. Triprolidine 10mg produced an overall increase of the peripheral reaction time, the difference with placebo reaching statistical significance on day 1, 8 hours after drug intake (p<0.05).

None of the other treatments however were found to be significantly different from placebo at any time point, (figure 5.22).
Figure 5.22: Compensatory Tracking Task – Reaction Time (msec)

Mean change from baseline (H0) on day 1 following the administration of ebastine, tripolidine and placebo

* = p<0.05 when compared to placebo
Compensatory Tracking Task (CTT) - Tracking Accuracy

In line with the above findings, the mean tracking accuracy scores (RMS), a different component of the SCTT, were significantly impaired at 8 hours following the administration of triprolidine on day 1 (p<0.05), (figure 5.23). Further testing on day 5 did not detect any significant placebo versus treatment differences on this task.

Figure 5.23: Compensatory Tracking Task - Tracking Accuracy

Mean change from baseline (HO) on day 1 following the administration of ebastine, triprolidine and placebo

* = p<0.05 when compared to placebo

(Eba = ebastine, Tri = triprolidine)
Sternberg Memory Scanning Task (SMST)

Significant treatment differences were evident with the SMST. Tripolidine 10 mg produced a clear decrement (increase in reaction time) on this measure of short term memory (fig 24), which was significantly different to placebo at 4 and 8 hours after drug administration (p<0.05). By day 5, the mean scores for all treatments were closely ranged together and no statistically significant differences were evident.

Figure 5.24: Sternberg Memory Scanning Task – Reaction time (msec)

Mean change from baseline (H0) on day 1 following the administration of ebastine, tripolidine and placebo

* = p<0.05 when compare to placebo

(Eba = ebastine, Tri = tripolidine)
LARS

The average of the three scores for ‘tired’, ‘drowsy’ and ‘alert’ of the LARS was used to
given an overall score of subjective sedation. Subjective reports of sedation were greatly
increased following triprolidine administration. At 2 and 4 hours after the first
administration of triprolidine, subjects felt clearly more sedated; this difference was
statistically significant when compared to placebo (p<0.05). Analysis of the LARS
results revealed no detectable effects of ebastine (10 & 20 mg) compared to placebo
(figure 5.24). However, ebastine administered at its highest dose of 30mg significantly
increased sedation scores at 4 hours on day 5 when compared to placebo (p<0.05),
(figure 5.25).

Figure 5.25: Line Analogue Rating Scales for Sedation – Mean change from
baseline (H0) on day 1 following the administration of ebastine,
triprolidine and placebo

* = p<0.05 when compared to placebo

(Eba = ebastine, Tri = triprolidine)
Figure 5.26: Line Analogue Rating Scales for Sedation (mm) - Mean change from baseline (H0) on day 5 following the administration of ebastine, triprolidine and placebo

* = p<0.05 when compared to placebo

(Eba = ebastine, Tri = triprolidine)
Analysis of the LSEQ results revealed significant placebo versus treatment differences for the night after the first administration only (p<0.05), indicating that both triprolidine and the highest dose of ebastine (30mg) had an effect on the ease of getting to sleep (GTS) (figure 5.27), while the effect on the quality of sleep (QOS) fell short of being significantly different from that seen under placebo (fig 5.28). None of the experimental treatments were found to interfere with the ease of waking from sleep (WFS) and the integrity of behaviour following waking (BFW). No placebo-treatment differences could be seen with regard to the night after the fifth administration.
Figure 5.27: Leeds Sleep Evaluation Questionnaire – Getting to Sleep: Mean change from baseline (H0) on days 2 & 6 following the administration of ebastine, triprolidine and placebo

* = p<0.05 when compared to placebo

(Eba = ebastine, Tri = triprolidine)
Figure 5.28: Leeds Sleep Evaluation Questionnaire - Quality of Sleep: Mean change from baseline (H0) on days 2 & 6 following the administration of ebastine, triprolidine and placebo

* = p<0.05 when compared to placebo

(Eba = ebastine, Tri = triprolidine)
5.6.4 Discussion of Results

Ebastine, at all three doses tested, was not significantly different from placebo in its effects on psychomotor performance and cognitive function. This is in contrast to the positive control, triprolidine, which produced significant impairment of cognitive and psychomotor function as measured by SCTT, SMST, LARS and LSEQ, for up to 8 hours after drug intake on day 1. However, impairment of performance tests and subjective reports of sedation lessened with repeated dosing and the detrimental effects of triprolidine were not detected at day 5, a finding which is consistent with previous literature (Bye et al 1977). This effect of triprolidine has been reported previously in a study in which the authors suggested the development of tolerance to the effects of triprolidine following repeated dosing. It was speculated that this effect was possibly a result of central receptors becoming less responsive to the drug or that different central homeostatic mechanisms served to counteract the induced sedation (Bye et al 1977). These present results are commensurate with previous published literature in which ebastine has been shown to be free of CNS adverse effects at doses up to 20 mg (Azcona et al 1992, Brookhuis et al 1993, Hopes et al 1992, Vincent et al 1988). Single oral doses of ebastine (10-30 mg) did not impair psychomotor performance, assessed by vigilance (EEG changes), cognitive performance, visual-motor co-ordination and subjective estimates of sedation in healthy volunteers (Hopes et al 1992, Mattila et al 1992, Vincent et al 1988a). Scores for all parameters were similar after placebo or ebastine administration, whereas the H₁-receptor antagonist, clemastine caused drowsiness, impairment of psychomotor performance, and had a selective effect on cognitive processes (Hopes et al 1992), and triprolidine significantly adversely affected aspects of driving ability compared to placebo (Brookhuis et al 1993). Ebastine 10 to 30 mg/day did not impair driving performance; however, doses above the therapeutic range (50-90
mg) caused sedation and impairment of performance, as evidenced by significantly increased reaction time at 4 and 8 hours, and a reduction in CFF threshold at 5.5 hours compared with placebo (Barbanoj et al 1988) (p<0.05). Using a battery of psychomotor tests and visual analogue scales (including a simulated driving test), investigators failed to find any effects of ebastine 10 or 20 mg/day for up to 7 days on the depressant activity of alcohol in healthy volunteers (Azcona et al 1992, Mattila et al 1992). A number of studies have reported subjective and objective evidence of sedation with high doses of ebastine and evidence exists to support the notion that ebastine does possess sedative activity when it is administered at doses higher than those recommended by the manufacturer (Barbanoj et al 1988, Vincent et al 1988a).

The present study, which was performed in 10 healthy female volunteers under double-blind, crossover conditions, was aimed at evaluating and comparing the central effects of three doses of ebastine with triprolidine, a sedative antihistamine known to produce cognitive and psychomotor impairments (Betts et al 1984, Brookhuis et al 1993, Riedel et al 1990a).

A positive control was included in the study to ensure the validity of the methods employed. The objective evaluation of the central effects did not show any significant modification with ebastine when compared with placebo and all the measurements were unchanged after ebastine intake irrespective of the dose and time after administration, a result which is in agreement with previous studies. In addition, there were no significant modifications in the subjective tests following the administration of the lower doses of ebastine (10-20mg). Following the repeated administration of the highest dose of ebastine, there were subjective reports of daytime tiredness on day 5, and a night-time 'sleep-inducing' effect after the first administration.
The general conclusion that can be drawn from the present study is that there were no significant objective effects on psychomotor performance following the administration of ebastine. This is in contrast to the effects of older, traditional AHs on various tests of psychomotor and cognitive function (Cohen et al 1985, Gengo et al 1987, Hindmarch & Shamsi 1999, Seidel et al 1987, Shamsi & Hindmarch 1999a).

Triprolidine included in this study as a positive control produced significant impairment between 4 and 8 hours after the first administration on objective measures (SCTT, SMST), and between 2 and 4 hours after the first administration on the subjective measures (LARS). This might indicate that antihistamine-induced sedation is subjectively experienced before it becomes evident in a performance test, and furthermore, that it is possible to tolerate and compensate for this sedation in performance tests so that impairment can not be detected objectively.

Although this study only uses ten subjects, the power is sufficient to show triprolidine acting as an internal control and ebastine having an effect only on the subjective rating scales. Given the importance of using AHs that are without unwanted CNS effects, confirmation of these findings should be made in a larger subject population. However, given this caveat, we have shown that ebastine at its recommended daily dose of 10 mg is free from disruptive effects on the CNS, in a study where the test battery proved sensitive to CNS impairment.
5.7 Experiment 7: The effects of hydroxyzine and lorazepam on cognitive function and sleep in patients with generalised anxiety disorder

5.7.1 Introduction & Rationale

The six previous experiments were conducted with healthy volunteers in which the cognitive and psychomotor profile of a number of second generation AHs were investigated.

However it is also important to investigate the cognitive and psychomotor effects of AHs in symptomatic patient populations who may or may not be already cognitively compromised as a result of the underlying disease.

Recently it has been shown that hydroxyzine is efficacious in relieving symptoms of anxiety in patients suffering from generalised anxiety disorder (Ferrelli et al 1995, Lader & Scotto 1998).

This experiment was therefore designed to assess the cognitive and psychomotor effects of hydroxyzine in patients suffering from generalised anxiety disorder.

For statistical purposes, the null hypothesis for the study was that neither hydroxyzine nor lorazepam would have any effects on cognitive and psychomotor function as assessed by a battery of valid, sensitive and reliable tests.

5.7.2 Methods & Measures

Subjects

Eighty one patients (35 male, 46 female), aged 21-71 years (median age of 42 years), were entered into the study. Inclusion criteria required the patients to meet the DSM IV criteria for GAD including excessive anxiety and worry, occurring more days than not for at least 6 months. Treatment with benzodiazepines in the previous two months or any
other psychoactive medication in the last month excluded the patients from participation in the study.

**Design**

The study was a randomised, double blind, parallel group, multi-centre design. Patients were randomised to receive a treatment for a period of 28 days. All medication was supplied in identical capsules and patients were instructed to take one dose in the morning, one at lunchtime and the third dose in the evening, half an hour before retiring to bed. Compliance was controlled by counting capsules returned by patients at each visit.

**Drugs**

Hydroxyzine 50mg/day in three divided doses (12.5mg/morning, 12.5mg/mid-day and 25mg/evening) or lorazepam 3mg in three divided doses (1mg/morning, 1mg/mid-day and 1mg/evening).

**Procedure**

Following informed consent, medical history and GP approval, all patients underwent a medical examination. Subject to fulfilling the inclusion/exclusion criteria, eligible patients were entered into the study and familiarised with the study procedures. Patients were required to attend the clinic (GP surgery) once a week for five weeks, in which they underwent a series of tests to measure the effects of hydroxyzine and lorazepam on cognitive function, memory recall, various aspects of sleep, clinical intensity of anxiety and the presence of any undesirable side effects. Pre-treatment
baseline recordings were then made on the first visit on each of the psychometrics (described below) and further testing was carried out on days 8, 15, 22 and 29.

As the consumption of alcohol in counter-indicated with hydroxyzine, patients were instructed to avoid alcohol during the trial period of 28 days.

Adverse events were recorded at each visit, with a description of frequency, nature, severity and causation. The use of all concomitant medication was also recorded at each visit.

**Test Battery**

The test battery consisted of Hamilton Anxiety Rating Scale (HAM-A), Cognitive Failures Questionnaire (CFQ), Clinical Global Impression (CGI), Critical Flicker Fusion (CFF), Milford Memory Test (MMT) and Leeds Sleep Evaluation Questionnaire (LSEQ).

**Statistical Analysis**

Due to the large number of dropouts in the lorazepam group, the two treatments could not be compared against one another and so each treatment was compared to its own baseline.

For all primary and secondary variables, apart from the LSEQ, the change from baseline was calculated and used in the analyses. The analysis of primary and secondary efficacy variables for the intention to treat (ITT) population was performed using paired ‘t’ tests to investigate within treatment differences. All statistical tests were two tailed at the 5% level of significance. In the intention to treat analysis, the Last Value Carried forward (LVCF) technique was used in the case of missing observations. If no such value was available, the baseline value was used.
5.7.3 Results

A high proportion (36%) of withdrawals occurred in the lorazepam group (n = 39) compared to the hydroxyzine group (12%) (n = 42). The majority of non-responders reported that they could not tolerate the side effects produced by lorazepam. As a result, all comparisons were made to each treatment’s own baseline and the two treatments could not be compared against one another.

The mean response data are presented in tables 27-33 of Appendix 1.

HAM-A

HAM-A overall scores were significantly decreased with both hydroxyzine and lorazepam. The mean decrease in scores for the hydroxyzine and lorazepam groups were 11.69 (t = 8.85 on 41 d.f., p < 0.001) and 7.01 (t = 5.33 on 38 d.f., p < 0.001) respectively (figure 5.29). In line with the overall HAM-A scores, both treatments showed a significant decrease in both the psychic and somatic elements of the HAM-A score.

Hydroxyzine showed a mean decrease of 3.76 on the psychic score (t = 6.65 on 41 d.f., p < 0.001) and 7.92 on the somatic score (t = 9.33 on 41 d.f.; p < 0.001) of the HAM-A whereas lorazepam produced a mean reduction of 1.94 (t = 4.23 on 38 d.f., p < 0.001) on the psychic score and 5.08 (t = 5.44 on 38 d.f.; p < 0.001) on the somatic score (figures 5.30 & 5.31).
Figure 5.29: HAM-A: Mean Overall Scores following the administration of hydroxyzine and lorazepam

* = p<0.001 compared to baseline
Figure 5.30: HAM-A Somatic Scores: Mean scores following the administration of hydroxyzine and lorazepam

* = p<0.05 when compared to baseline
Figure 5.31: HAM-A Psychic Scores: Mean scores following the administration of hydroxyzine and lorazepam

* = p<0.05 when compared to baseline
Cognitive Failures Questionnaire

Cognitive failures questionnaire scores showed a significant improvement with hydroxyzine at days 15 (t = 3.27 on 41 d.f., p<0.005), 22 (t = 2.82 on 41 d.f., p<0.01) and 29 (t = 3.31 on 41 d.f., p<0.005). In contrast, there were no changes in the CFQ score following the administration of lorazepam (figure 5.32).

Figure 5.32: Cognitive Failures Questionnaire: Mean change from baseline following the administration of hydroxyzine and lorazepam

* = p<0.01 when compared to baseline

** = p<0.005 compared to baseline
Clinical Global Impression

Clinical global impression results were indicative of significant improvements with hydroxyzine in both cognitive function and quality of sleep. Cognitive function was rated as significantly improved at day 29 (t = 2.90 on 40 d.f., p < 0.01) (figure 5.33), whereas there were significant improvements in the physician rated quality of sleep at all visits for both drugs (figure 5.34). There were no significant changes in cognitive function reported with lorazepam, although the quality of sleep was significantly improved at all visits.

Figure 5.33: Clinical Global Impressions - Cognitive Function

Mean change from baseline following the administration of hydroxyzine and lorazepam

* = p < 0.01 compared to baseline

Mean CGI Score

-1 -0.5 0 0.5 1

Day

- Lorazepam  - Hydroxyzine
Figure 5.34: Clinical Global Impressions – Quality of Sleep

Mean change from baseline following the administration of hydroxyzine and lorazepam

* = p< 0.05 compared to baseline
CFF

No significant impairments were detected with CFF in the lorazepam group (figure 5.35). However, an impairment in scores was evident with hydroxyzine at days 8 ($t = 2.90$ on 41 d.f., $p < 0.01$) and 15 ($t = 2.84$ on 41 d.f., $p < 0.01$).

Figure 5.35: Critical Flicker Fusion (Hz) – Mean change from baseline following the administration of hydroxyzine and lorazepam

$*$ = $p < 0.05$ when compared to baseline
**Milford Memory Test**

Analysis of the Milford Memory Test results showed improved performance with hydroxyzine in a number of tasks including the shopping list recall, names to faces and forward and backward digit span, (table 5.13).

Hydroxyzine caused improvements in the shopping list recall task at day 29 (t =2.45 on 41 d.f., p=0.018), whereas lorazepam produced impairments on this task (t =4.27 on 38 d.f., p<0.001) on day 8 (figure 5.36). Significant improvements were evident on the names to faces task at day 22 (t = 2.25 on 41 d.f., p=0.029) following the administration of hydroxyzine. No significant changes were evident following lorazepam treatment.

The forward recall of digits was significantly improved following hydroxyzine (figure 5.37) at day 15 (t =2.84 on 41 d.f., p<0.01) and 22 (t =2.89 on 41 d.f, p<0.01).

Significant improvements were also reported at day 8 (t =2.35 on 41 d.f; p<0.05) for the backward recall of digits following hydroxyzine. Lorazepam treatment did not result in significant changes in this task.
Table 5.13: Milford Memory Test: Mean values (standard errors) following the administration of hydroxyzine and lorazepam

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day</th>
<th>Shopping List Recall</th>
<th>Shopping List Choice Recognition</th>
<th>Picture of Objects</th>
<th>Picture of Objects Choice Recognition</th>
<th>Names to Faces</th>
<th>Digit Span (forward)</th>
<th>(Digit Span) backward</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyzine</td>
<td>1</td>
<td>7.19 (0.23)</td>
<td>9.40 (0.18)</td>
<td>7.76 (0.20)</td>
<td>9.59 (0.14)</td>
<td>9.60 (0.47)</td>
<td>6.86 (0.21)</td>
<td>5.36 (0.21)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>6.93 (0.20)</td>
<td>8.98 (0.22)</td>
<td>7.88 (0.25)</td>
<td>9.62 (0.90)</td>
<td>10.17 (0.52)</td>
<td>7.00 (0.21)</td>
<td>5.83 (0.26)*</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>6.86 (0.24)</td>
<td>9.36 (0.16)</td>
<td>7.33 (0.21)*</td>
<td>9.81 (0.10)</td>
<td>9.81 (0.45)</td>
<td>7.38 (0.22)*</td>
<td>5.57 (0.26)</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>7.48 (0.28)</td>
<td>9.40 (0.18)</td>
<td>7.57 (0.22)</td>
<td>9.67 (0.10)</td>
<td>10.48 (0.46)*</td>
<td>7.38 (0.20)*</td>
<td>5.62 (0.23)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>7.71 (0.21)*</td>
<td>9.48 (0.13)</td>
<td>8.19 (0.21)*</td>
<td>9.76 (0.67)</td>
<td>10.11 (0.45)</td>
<td>7.07 (0.20)</td>
<td>5.64 (0.21)</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1</td>
<td>7.05 (0.21)</td>
<td>9.13 (0.25)</td>
<td>7.67 (0.22)</td>
<td>9.62 (0.13)</td>
<td>8.92 (0.44)</td>
<td>6.46 (0.26)</td>
<td>4.56 (0.31)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>6.00 (0.26)*</td>
<td>8.97 (0.19)</td>
<td>7.67 (0.23)</td>
<td>9.41 (0.13)</td>
<td>9.23 (0.49)</td>
<td>6.54 (0.25)</td>
<td>4.92 (0.29)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>6.59 (0.26)</td>
<td>9.31 (0.16)</td>
<td>7.51 (0.26)</td>
<td>9.64 (0.11)</td>
<td>9.54 (0.54)</td>
<td>6.40 (0.26)</td>
<td>4.74 (0.32)</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>6.64 (0.30)</td>
<td>9.46 (0.18)</td>
<td>7.10 (0.26)</td>
<td>9.82 (0.89)</td>
<td>9.62 (0.55)</td>
<td>6.62 (0.26)</td>
<td>5.05 (0.32)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>6.85 (0.27)</td>
<td>9.46 (0.17)</td>
<td>7.85 (0.29)</td>
<td>9.74 (0.10)</td>
<td>9.56 (0.57)</td>
<td>6.56 (0.25)</td>
<td>4.77 (0.31)</td>
</tr>
</tbody>
</table>

* = p<0.05 when compared to baseline
Figure 5.36: Milford Memory Test - Shopping List Recall

Mean change from baseline following the administration of hydroxyzine and lorazepam

* = p<0.05 when compared to baseline
Figure 5.37: Milford Memory Test - Digit Span (Forwards)

Mean change from baseline following the administration of hydroxyzine and lorazepam

\* = p<0.05 when compared to baseline
Analysis of the LSEQ results demonstrated that neither treatment group significantly affected getting to sleep nor the quality of sleep measures of the LSEQ. The awakening from sleep was significantly improved from visit 3 (F(3, 117) = 4.964, p < 0.01) following hydroxyzine administration (figure 5.38).

Figure 5.38: Leeds Sleep Evaluation Questionnaire – Awakening from Sleep

Mean change from baseline following the administration of hydroxyzine and lorazepam

* = p < 0.05 when compared to baseline
5.7.4 Discussion

The aim of this study was to investigate the effects of hydroxyzine 50mg and lorazepam 3mg on cognitive function and various aspects of sleep in patients suffering from GAD. The results demonstrate that hydroxyzine and lorazepam were both efficacious in alleviating symptoms of anxiety as assessed by the HAM-A rating scales. However, a high proportion of withdrawals occurred in the lorazepam group (36%) compared to the hydroxyzine group (12%). The majority of non-responders reported that they could not tolerate the side effects produced by lorazepam. This result is consistent with previous findings in which side effects such as cognitive impairments, memory loss, withdrawal and dependence have been demonstrated with benzodiazepines (BDZs) including lorazepam (Hindmarch & Gudgeon 1980, Hindmarch & Tiplady 1994, Simon & Pollack 1998, Subhan et al 1986).

As regards the effects on cognitive function, differences were evident on a number of tasks following both treatments. As CFF is an indicator of central processing ability, it was expected that the administration of lorazepam would be associated with a decrease in CFF thresholds. However, no impairments were observed with CFF in this group. In line with this finding, cognitive failures questionnaire scores were not significantly affected by lorazepam and no significant changes in cognitive function were reported with the clinical global impression. Similarly, various tasks of the MMT such as the forward and backward recall of digits, picture of objects, names to faces task did not demonstrate any detrimental effects following the administration of lorazepam but significant impairments were demonstrated on the shopping list recall task at day 8. There were no significant effects on any aspects of the LSEQ.
These current findings with lorazepam are surprising given the fact that the drug is well known to impair memory (Curran 1998, Preston et al 1992), produce sedation (Hindmarch & Gudgeon 1980, Hindmarch & Tiplady 1994), and disrupt cognitive and psychomotor abilities in general (Subhan et al 1986).

Of the eighty one patients randomised into the study, fourteen patients (36%) in the lorazepam group and five (12%) in the hydroxyzine group dropped out and did not complete the study. The majority of dropouts could not tolerate the side effects produced by lorazepam. It is also possible that the remaining patients who could actually tolerate the unwanted side effects of lorazepam were resistant to its effects.

The most likely explanation is that the severity of the side effects may have led to non-compliance. Although compliance was checked at every visit by counting the number of tablets returned, this is by no means an absolute indicator of drug intake. It was evident from the CFF results that the scores did not change throughout the 28 day period. This was further supported by lack of cognitive impairments reported by patients on the CFQ, CGI and various tasks of the MMT. It was also interesting that there were no significant differences reported on any aspect of the LSEQ, considering the sedative profile of lorazepam. Whatever the reason for these findings, it was clear that no comparisons could be made between the two treatments and it was for this reason that it was decided to perform a within treatment analysis in which differences for each treatment group were compared to baseline.

Contrary to the findings with lorazepam, improvements were evident following the administration of hydroxyzine on a number of tasks throughout the 4 week treatment period.

Results from the cognitive failures questionnaire clearly indicated an improvement over the 4 week period following the administration of hydroxyzine. This finding was further
supported with the results of the clinical global impression, in which physicians indicated significant improvements at days 8 and 15. In line with this, the quality of sleep aspect of the CGI was significantly improved throughout the 4 week treatment period. Performance on a number of tasks of the MMT such as the shopping list recall, picture of objects recall, forward and backward recall of digits clearly demonstrated an improvement following the administration of hydroxyzine throughout the 4 week treatment period. Although the getting to sleep and quality of sleep aspect of the LSEQ were not significantly affected by hydroxyzine, significant improvements were reported with hydroxyzine for the awakening from sleep aspect of the LSEQ from day 15. Despite the reported improvements on a number of tasks with hydroxyzine, CFF scores were significantly reduced at days 8 and 15. However the maximum decrease in thresholds, although statistically significant when compared to baseline, was 0.85Hz. The clinical significance of this decrease is questionable as a number of factors such as diurnal variation, time of day effect or an interaction of these and other variables could account for this finding.

The impairment of cognitive function is an important factor to consider when treating anxious patients. Firstly, the majority of patients suffering from anxiety are out patients and any impairment caused could increase the likelihood of accidents. Secondly, anxious patients are cognitively compromised and therefore the administration of a psychoactive compound known to cause impairments can be counter-therapeutic as it exacerbates the existing problems. Therefore if a patient is going to be effectively treated by pharmacotherapy, then a non-behaviourally toxic anxiolytic not only produces a good clinical response, but also ensures that patients are free from unwanted secondary side effects (Shamsi & Hindmarch 1999).
In view of the emphasis on maintaining the integrity of cognitive functions during treatment with anxiolytics, it is interesting to note that in a controlled study, treatment of GAD patients with hydroxyzine 100mg/day for a month showed better and more rapid improvement of cognitive functioning, when compared to lorazepam 4mg/day as assessed by Beck scale (Samuelian et al 1995). A placebo-controlled study revealed that in contrast to lorazepam (2mg), hydroxyzine (50mg) did not affect short and long term memory span. In the measurement of verbal memory using 15 Words of Rey, no difference was observed between the number of words remembered under hydroxyzine and placebo, compared with fewer words with lorazepam, indicating that hydroxyzine causes no attention deficit or impairment of immediate memory (De Brabander & Debert 1990). Another study using continuous EEG and a number of validated psychometric tests including the critical flicker fusion task (CFF) showed that hydroxyzine at 25mg or 50mg did not result in psychological dysfunction either immediately or the next day. In addition, unlike many BDZs, hydroxyzine did not impair short-term memory the morning following nocturnal administration (Ferretti & Hantouche 1998).

Despite the demonstration of hydroxyzine's efficacy in GAD (Ferretti et al 1995, Lader & Scotto 1998, Samuelian et al 1995), the mechanisms of the anxiolytic effects are not well understood. However it is known that antihistamines primarily affect hyperarousal (Hoehn-Saric 1998). An 'inverted U' relationship exists between behavioural arousal and performance. If hyperarousal is responsible for the poor cognitive performance of anxious patients, then a small reduction in arousal by hydroxyzine may improve cognition by shifting them along and up the performance curve. In contrast the profound sedative action of most of the 1,4-BDZs reduces arousal to such an extent that performance remains poor and cognitive functioning is compromised (Hindmarch et al 1999).
This present study broadly supports these findings and shows that hydroxyzine has no significant detrimental effects, which would permit the full therapeutic value of the drug to be realised.
CHAPTER 6 MEASUREMENT OF DRUG ACTION IN MAN: PSYCHOMETRIC ASPECTS OF ANTIHISTAMINES: RESULTS AND CONCLUSIONS

6.0 Chapter Outline

The preceding chapter outlined the results of the experimental studies. The findings of the results together with the relevance of these findings are discussed in terms of the impact they may have on the management of allergic disorders.

6.1 Introduction

Chapter one provided an introduction to the AHs and highlighted that despite achieving their greatest therapeutic role in the treatment of various allergic disorders, the use of AHs, especially those of the first generation category, is commonly associated with a number of undesirable side effects, the most troublesome of which is sedation. A review of the literature including experimental studies with all AHs in healthy volunteers demonstrated the detrimental CNS effects following the administration of all first generation AHs at all doses. Furthermore, the review identified a number of second generation AHs with which objective and subjective evidence of CNS impairment became apparent when administered at higher doses. Of the 23 AHs investigated in the review, fexofenadine at doses up to 240mg was shown to be significantly different to all other AHs as regards its effects on aspects of cognitive functioning and psychomotor performance (PIR value of 0.00, \(X^2 =14.50, p<0.001\)), thus providing further support to the notion that it should be classed as a ‘third generation’ antihistamine, at least as regards its unique profile of lack of CNS effects.

In investigating the sensitivity of the psychometrics to antihistamine-induced impairment, the overall findings were disappointing, in that only three categories of tests
were identified as useful for discriminating between AHs as regards their potential to cause cognitive and psychomotor impairment. Many individual tests were used infrequently and data from these tests did not represent a broad range of AHs. With certain tests, despite an overtly clear categorisation (e.g. CFF), it was not possible to guarantee that the apparatus used to measure the threshold was identical in all studies and as Bobon (1982) reports, there is more disagreement between CFF results and certain psychometric tests due to the equipment used to measure the threshold than any other source of variance. Furthermore, other intervening variables such as time course of pharmacodynamic action, time of test administration etc. could not be taken into account for the overall analysis, as it would have fragmented the available data even further.

In order to reduce these sources of variability and allow conclusions about the sensitivity of psychometric tests, the findings with all first generation AHs used in the review were pooled together.

Tests of car driving, reaction time and subjective assessments were the only three categories, which were shown to obtain a significant proportional impairment detection ratio (PIDR). However, tests of car driving were used too infrequently and the parameter under investigation was the standard deviation from lateral position (SDLP). According to the hierarchical structure of the driving task proposed by Janssen (1979) however, tests of car driving in which the parameter under investigation is the SDLP should be assigned exclusively to the lowest hierarchical level, i.e. the control level, since only the course-keeping tasks are evaluated and important functions such as attention, judgement and coordination are not assessed (Willumeit et al 1993).

The clinical review surveyed and analysed the data on the incidence of subjectively reported sedation in patient studies with AHs in order to investigate the value and accuracy of patient reports with regard to antihistamine-induced sedation. The analysis
of this selected sample of studies confirmed the general consensus published in numerous articles and reviews, namely that second generation AHs were relatively free from sedation when compared to the traditional AHs which were associated with frequent subjective reports of sedation.

It was therefore concluded that the compilation of subjective reports obtained in clinical studies with AHs, even though not standardised, were not to be discarded as a means for gathering information on the sedative potential of AHs. It was also evident that patients seemed to be able to discriminate successfully between AHs with and without sedative effects, despite the lack of validated assessment tools available for such assessments in the clinical setting.

As the majority of the studies which were analysed in this review were conducted using a parallel group design, it could not be guaranteed that the subjects comprising the placebo and the antihistamine treatment groups were comparable in terms of their sensitivity to antihistamine-induced sedation. Nevertheless, it was assumed that the relatively large number of patients per treatment group in these studies was able to compensate for the variability due to intraindividual differences in sensitivity to AHs.

Although this analysis demonstrated that subjective reports in clinical studies can successfully distinguish between first and second generation AHs, it was felt that there was scope for more objective and refined ways of assessing antihistamine-induced sedation.

In clinical studies the perceived clinical effect, or lack of it, may have partly unblinded the patients and affected the outcome. In some cases, a perceived lack of a clinical effect could have caused the subjects to report no side effects. It is clear that the vagaries of psychological reporting of subjective experiences would make any outcome possible (Rombaut 1995).
6.3 Summary of Experimental Studies

A series of controlled experiments in non-atopic volunteers investigated the effects of a number of second generation AHs on various aspect of cognitive functioning and psychomotor performance. In addition to these, an additional experiment was conducted to investigate the cognitive and psychomotor effects of hydroxyzine and lorazepam in patients suffering from generalised anxiety disorder.

Experiment 1 demonstrated that a low dose of fexofenadine (40mg b.d.) was as effective as loratadine 10mg in suppressing the histamine-induced weal and flare response. Although there were no significant differences between the two treatments, both were superior to placebo in their peripheral blocking effects. Experiment 2 was a follow-up of the previous study, in which the peripheral blocking effects of higher doses were compared with loratadine and promethazine in a double-blind placebo-controlled crossover study. Fexofenadine (120mg & 180mg) was shown to be significantly superior to loratadine 10mg with regards to speed of onset, duration of effect and the time taken to achieve maximum suppression of the skin weal and flare response. These findings are in agreement with previous research in which 120mg fexofenadine has been shown to have a faster onset of action than loratadine (Simons et al 1997).

Having established the peripheral blocking effect of fexofenadine, the CNS profile of fexofenadine at doses up to 180mg was investigated in a double blind placebo controlled cross-over study in which loratadine was included as a comparator and promethazine as a positive internal control (experiment 3). Results clearly indicated the lack of impairments with fexofenadine at doses up to 180mg using a battery of tests, which clearly indicated the detrimental effects of the positive internal control.

Experiment 4 investigated the central effects of three equipotent doses of cetirizine and loratadine. Impaired performance was demonstrated with the positive control. Cetirizine
at all doses tested was free of CNS impairing effects, whereas the highest dose of loratadine (40mg) caused an increase in reaction time.

Experiment 5 investigated the central effects of single doses of ebastine at doses up to 40mg. Impairments were demonstrated with the positive control as well the highest dose of ebastine on a number of tests, indicating that although ebastine is free of adverse CNS effects at its recommended dose of 10mg, detrimental effects become evident when this dose is exceeded.

Experiment 6 was an extension of the previous experiment in which the effects of repeated dosing of ebastine at doses up to 30mg were investigated in a group of healthy volunteers. The results of this experiment lend further support to the conclusions made about the CNS profile of ebastine in the previous experiment.

Experiment 7 was distinct from the others in that it was conducted in patient populations within a general practice setting. Hydroxyzine and lorazepam were both shown to be alleviated symptoms of anxiety as assessed with the Hamilton Anxiety Rating Scale. Hydroxyzine was well tolerated and patients reported improvements in their cognitive functioning following treatment with hydroxyzine. This improvement was also objectively documented using a battery of tests.

Overall, the positive controls (promethazine and tripolidine) behaved as expected in that they consistently impaired performance on a number of different tests used across the different studies. The second generation AHs were shown to be free of CNS adverse effects when administered within their ‘dose window’. Impairments became evident on both objective and subjective measures when these doses were exceeded. The higher doses of loratadine (20mg & 40mg) and ebastine (20mg, 30mg & 40mg) caused significant CNS impairments, whereas cetirizine (at doses up to 10mg) and fexofenadine
(at dose up to 180mg) were demonstrably free of detrimental effects on various aspects of cognitive and psychomotor performance.

6.4 Conclusions and Recommendations for Future Research

As AHs are widely used for the treatment of allergic disorders such as seasonal allergic rhinitis (SAR), then such usage is mainly by ambulant patients including children, and any CNS effects could compromise performance and safety. In addition to efficacy, the side effect profile of an antihistamine should therefore be the second most important aspect to be considered.

It is generally accepted that there is little to choose between AHs in terms of efficacy. The evidence gathered in the literature review and the experimental data presented in this thesis suggest, however, that there are differences in the extent to which these drugs influence performance.

The extensive review of the clinical data as well as experimental studies with AHs in healthy volunteers clearly demonstrated the significant detrimental CNS effects of the traditional AHs. The differences between the second generation AHs, however, did not appear to be so clear cut, although it was clearly evident that the use of the second generation AHs also resulted in cognitive and psychomotor impairment especially when higher doses were used.

The conclusions to be drawn from this work are that the administration of the first generation AHs is frequently associated with performance impairments, whereas the second generation AHs cause detrimental CNS side effects when higher doses are administered. To date, fexofenadine is the only antihistamine, which at doses up to 240mg is free from adverse CNS effects.
Despite the lack of CNS effects at doses up to 240mg in a number of well designed and adequately controlled studies with fexofenadine, further research is required with this antihistamine at higher doses.

Other second generation antihistamines such as cetirizine and loratadine have been investigated at doses up to four times the recommended dose regimen. It is therefore crucial to investigate the CNS profile of fexofenadine at doses of 360mg & 480mg.

In addition, the effects of co-administration with alcohol must be studied with this antihistamine at various doses. The central effects of fexofenadine following repeated administration should also be investigated.

Actigraphy appears to be a useful tool in the measurement of drug action, and so future experiments should utilise this measure in order to allow continuous monitoring of activity, in addition to psychometric testing at discrete time points.

Sleep disturbance often occurs in patients with chronic allergic disorders such as chronic idiopathic urticaria, and therefore the investigation of the effects of these compounds on sleep should provide interesting and useful data.

If future research into the effects of AHs follows standardised designs and procedures, and adopts an accepted battery of measurements such as those outlined in this thesis, it would be possible to perform a meta-analysis of the effects of AHs on performance, thereby creating international indices of behavioural toxicity which would subsequently allow the classification of the AHs into three distinct groups; AHs with which sedation is experienced at all doses, AHs with which sedation becomes apparent when higher doses are administered and finally AHs devoid of adverse CNS effects regardless of the administered dose.
Evaluation of cetirizine in patients with allergic rhinitis and perennial asthma.
Annals of Allergy, Asthma and Immunology, 76 (5), 440-446.

Rational use of antihistamines in allergic dermatological conditions.
Drugs, 38(4), 634-644.

Pharmacokinetics of D8- tetrahydrocannabinol in man after smoking: relations to
physiological and psychological effects.
In: Brant, M.and Szara T.S. (Eds.)
Pharmacology of Marihuana, Raven Press, New York.

Selective displacement of [3H] mepyramine from peripheral versus central nervous
system receptors by loratadine, a non-sedating antihistamine.

Measurement of feelings using visual analogue rating scales.
Proceedings of the Royal Society of Medicine, 62, 989-993.

A comparison of antihistamines using EEG and questionnaire based assessments.
Medical Science Research, 17, 421-423.

Cetirizine versus astemizole in the treatment of chronic idiopathic urticaria.
Journal of International Medical Research, 18, 358-365.

Astemizol y terfenida em rinite alergica perene.
A Fohla Medica, 96, 125-130.

A double blind placebo controlled study of the efficacy and tolerability of ebastine
against hay fever in general practice patients.
Journal of Internal Medicine, 226, 453-458.

Arendt, C. and Bernheim, J. (1989)
Double blind comparison of maintenance treatment of chronic idiopathic urticaria by
cetirizine and terfenadine.
Current Therapeutic Research, 46 (4), 724-734.
Auto-inhibition of histamine release mediated by a novel class \((H_3)\) of histamine receptors.

Absence of central effects with levecabastine eye drops.
Allergy, 45, 552-554.

Receptors mediating some actions of histamine.
British Journal of Pharmacology & Therapeutics, 27, 247-249.

Ayd, F.D. (1972)
Motivations and rewards for volunteering to be an experimental subject.
Clinical Pharmacology and Therapeutics, 13, 771-781.

Evaluation of the CNS effects of repeated doses of ebastine and their interaction with alcohol in healthy subjects. (abstract)

Double blind comparison of levocabastine eye drops with sodium cromoglycate and placebo in the treatment of seasonal allergic rhinoconjunctivitis.
Clinical and Experimental Allergy, 21, 689-694.

Terfenadine in allergic rhinitis. A comparative trial of a new antihistamine versus placebo.
The Practitioner, 226, 347-351.

Treatment of seasonal allergic rhinitis with flunisolide and terfenadine.
Journal of International Medical Research, 14, 35-41.

Backhouse, C.I. and Rosenberg, R. (1987)
Prophylaxis of whole season hay fever symptomatology: a comparison of terfenadine with chlorpheniramine.
British Journal of Clinical Practice, 41, 995-999.

Backhouse, C.I., Rosenberg, R.M. and Fidler, C. (1990a)
Treatment of seasonal allergic rhinitis: a comparison of a combination tablet of terfenadine and pseudoephedrine with the individual ingredients.
A retrospective study of promethazine and its failure to produce the expected incidence of sedation during space flight.

Comparative efficacy of once daily loratadine versus terfenadine in the treatment of allergic rhinitis.
Journal of International Medical Research, 17, 150-156.

Psychomotor performance after different single oral doses of a new non-sedating antihistamine in healthy subjects.
Allergy Proceedings, 746.

Barlow, J.L.R., Beitman, R.E. and Tsai, T.H. (1982)
Terfenadine safety and tolerance in controlled trials.
Drug Research, 32, 1215-1217.

Bateman, D.N. and Rawlins, M.D. (1984)
Clinical pharmacology of astemizole.
In: Astemizole: a new, non-sedative, long acting antihistamine.

The effects of diphenhydramine alone and in combination with ethanol on histamine skin response and mental performance.
European Journal of Clinical Pharmacology, 12, 201-204.

Baurle, G. (1985)
Heuschnupfen Therapie mit zwei sedierungsfreien antihistaminika.
Zeitschrift fur Hautkrankheiten, 60, 46.

Bedard, P.M., Del Carpio, J., Drouin, M.A., Yang, W., Herbert, J., Lavoie, A., Prevost, P.M., Turenne, Y., PetitClerc, C. and Lorber, R. (1992)
Onset of action of loratadine and placebo and other efficacy variables in patients with seasonal allergic rhinitis.
Clinical Therapeutics, 14 (2), 268-275.

Comparative effects of loratadine and terfenadine in the treatment of chronic idiopathic urticaria.
Annals of Allergy, 64 (ii), 191-194.

Topical levocabastine, a selective histamine antagonist in seasonal allergic rhinoconjunctivitis.
Allergy, 42, 512-515.
The effectiveness of the non-sedating antihistamine loratadine plus pseudoephedrine in the symptomatic management of common cold.
Annals of Allergy, 63, 336-339.

Comparison of efficacy, safety and skin test inhibition of cetirizine and astemizole.
Annals of Allergy, Asthma and Immunology, 76, 363-368.

Estudo duplo-ciego entre astemizol e terfenida no tratamento da urticaria cronica.
A Fohla Medica, 99, 295-300.

Fexofenadine: A new non-sedating antihistamine is effective in the treatment of seasonal allergic rhinitis. (abstract)
Journal of Allergy and Clinical Immunology, 97 (1/3): 1010.


Efficacy and safety of astemizole, a long acting and non-sedating H1 antagonist for the treatment of chronic idiopathic urticaria.
Journal of Allergy and Clinical Immunology, 77, 37-42.

Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis.
Annals of Allergy, Asthma and Immunology, 79 (5), 443-532.

Bertrand, B., Clement, P. and Daele J. (1990)
Double blind parallel group comparison of once a day terfenadine and loratadine in seasonal allergic rhinitis, a multicentre study.
Acta Therapeutica, 16, 351-360.

Beswick, K.J.B., Kenyon, G.S. and Cherry, J.R. (1985)
A comparative study of beclomethasone dipropionate aqueous nasal spray with terfenadine tablets in seasonal allergic rhinitis.
Current Medical Research and Opinion, 9, 560-567.

A comparison of the effects of two non-sedating antihistamines (terfenadine and cetirizine) on tests of CNS function including driving.
Effects of two antihistamine drugs on actual car driving performance.

A double blind, single dose study of the effects of loratadine on driving skills in normal
volunteers. (abstract).
XIII International Congress of Allergology and Clinical Immunology, Montreux.

The effects of terfenadine with and without alcohol on aspects of car driving
performance.
Clinical and Experimental Allergy, 19, 609-611.

Biehl, B. (1979)
Effects of azatadine maleate on subjective appraisal and psychomotor functions relevant
to driving performance.
Current Medical Research and Opinion, 6, 62-69.

Double blind studies with levocabastine, sodium cromoglycate, and placebo in the topical
treatment of children with allergic conjunctivitis.
In: Mygind, N. and Naclerio, R.M. (eds.)
Hogrefe and Huber Publishers, Toronto, 49-52.

Definition and antagonism of H2 receptors.

Blamoutier, J. (1978)
Comparative trial of two antihistamines: mequitazine and brompheniramine.
Current Medical Research and Opinion, 5 (5), 366-367.

Critical Flicker Fusion Frequency. Introduction to the CINF session in Goteborg and
methodological recommendations.
Pharmacopsychiatry, 15 (suppl 1), 1-4.

Boggs, P.B., Ellis, C.N., Grossman, J., Washburne, W.F., Gupta, A.K., Ball, R. and
Double blind placebo controlled study of terfenadine and hydroxyzine in patients with
chronic idiopathic urticaria.
Annals of Allergy, 63, 616-620.

Boland, N. (1988)
A double blind study of astemizole and terfenadine in the treatment of perennial rhinitis.
Annals of Allergy, 61, 18-24.
The use of analogue rating scales in rating subjective feelings.
British Journal of Medical Psychology, 47, 211-218.

Efficacy and safety of loratadine suspension in the treatment of children with allergic rhinitis.
Allergy, 44, 437-441.

Evaluation de la cetirizine et de la terfenadine dans la traitement de la rhinite allergique perennuelle.
Acta Oto-Rhino-Laryngologica, 43, 75-81.

Bonvier, R., Borras, J. and Chalmagne, J. (1986)
Evaluation of the therapeutic effect of astemizole in perennial allergic rhinitis.
Current Therapeutic Research, 39, 244-249.

Effects of diphenhydramine on subjective sleep parameters and on motor activity during bedtime.
International Journal of Pharmacology, Therapy and Toxicology, 26 (8), 392-396.

Visual motor cross-over-ordination and dynamic visual acuity.
British Journal of Clinical Pharmacology, 69s-72s.

Assessment of quality of life in patients with perennial allergic rhinitis with the French Version SF36 Health Status Questionnaire.
Journal of Allergy and Clinical Immunology, 94, 182-188.

Double blind multicentre study of cetirizine in grass pollen-induced asthma.
Annals of Allergy, 65, 504-508.

Antiallergic activity of H1 receptor antagonists as assessed by nasal challenge.
Journal of Allergy and Clinical Immunology, 82, 881-887.

Bovet, D. and Straub, A. (1937)
Action protectrice des ethers phenoliques au cours de l’intoxication histaminique.
Compte Rendu des Seances de la Societe de Biologie (Paris), 124, 547-549.

Studies on the central effects of the H1 antagonist, loratadine.
Clinical studies of terfenadine in seasonal allergic rhinitis.
Arzneimittel Forschung, 32, 1204, 1205.

Cetirizine versus hydroxyzine and placebo in chronic idiopathic urticaria.
Annals of Pharmacotherapeutics, 30 (10), 1075-1079.

Summary of four clinical trials with terfenadine.
Drug Research, 32, 1213-1214.

The cognitive failures questionnaire (CFQ) and its correlates.
British Journal of Clinical Psychology, 21, 1-16.

Perennial rhinitis, treated by astemizole.

Bronsky, E., Boggs, P., Findlay, S., Gawchik, S., Georgitis, J., Mansmann, H., Sholler, L., Wolfe, J., Meltzer, E., Morris, R., Munk, Z., Paull, B., Pleskow, W., Ratner, P.,
Comparative efficacy and safety of a once-daily loratadine-pseudoephedrine combination versus its components alone and placebo in the management of seasonal allergic rhinitis.
Journal of Allergy and Clinical Immunology, 96 (2), 139-147.

Effectiveness and safety of fexofenadine, a new non-sedating antihistamine, in the treatment of fall allergies.
Allergy Asthma Proceedings, 19 (3), 135-141.

Acute and subchronic effects of histamine (H1) receptor antagonist ebastine in 10, 20 and 30mg dose, and tripolidine 10mg on car driving performance.
British Journal of Clinical Pharmacology, 36, 67-70.

Controlled trial of terfenadine and chlorpheniramine maleate in perennial rhinitis.
Postgraduate Medical Journal, 58, 422-423.

Prolonged treatment with acriavistane for seasonal allergic rhinitis.
Journal of International Medical Research, 17, 40B-46B.
Valutazione in doppio cieco degli effetti dell’astemizolo nel trattamento della rino
patia allergica.
Il Progresso Medico, 37, 856-860.

Bruttman, G., Arendt, C. and Bernheim, J. (1989a)
Double blind placebo controlled comparison of cetirizine 2HCl and terfenadine in atopic
dermatitis.

Evaluation of efficacy and safety of loratadine in perennial allergic rhinitis.
Journal of Allergy and Clinical Immunology, 83, 411-416.

Loratadine 40mg once daily versus terfenadine 60mg twice daily in the treatment of
seasonal allergic rhinitis.
Journal of International Medical Research, 15, 63-70.

Protective effect of cetirizine in patients suffering from pollen asthma.
Annals of Allergy, 64, 224-228.

Bryant, B.G. and Lombardi, T.P. (1993)
Cold, cough and allergy products.
Pharmaceutical Products.

Dose response of prick skin test suppression by ebastine.
Journal of Allergy and Clinical Immunology, 92, 163.

Buckley, C.E., Buchanan, E., Falliers, C.J., Segal, A.T., Tinkelman, D.G., Wray, B.B.,
Terfenadine treatment of fall hay fever.
Annals of Allergy, 60, 123-127.

Treatment of allergic rhinitis with a new selective H1 antihistamine: terfenadine.
New England and regional Allergy proceedings, 6, 63-70.

Evidence for the tolerance to the central nervous effects of the histamine antagonist,
triprodilide, in man.
European Journal of Clinical Pharmacology, 12, 181-186.
Effects on the human central nervous system of two isomers of ephedrine and tripolidine, and their interaction.
British Journal of Clinical Pharmacology, 1, 71-78.

Double blind comparison of astemizole and terfenadine in the treatment of chronic urticaria.
Pharmatherapeutica, 4, 679-685.

Correlation between plasma diphenhydramine level and sedative antihistaminic effects.
Clinical Pharmacology and Therapeutics, 23, 375-382.

Item recognition as a performance evaluation test for environmental research.

Cassale, T.B. (1999)
Safety and effectiveness of once-daily dosing of fexofenadine HCl in the treatment of seasonal allergic rhinitis. (abstract)
Journal of Allergy and Clinical Immunology, 103 (1 part 2), S253, abs 971.

Treatment of chronic idiopathic urticaria with terfenadine.
Clinical Allergy, 14, 139-141.

Comparative, double blind study of cetirizine and astemizole in the treatment of allergic rhinitis.
Journal of Allergy and Clinical Immunology, 85, 243.

Once daily loratadine versus astemizole once daily.
Annals of Allergy, 73, 109-112.

Levocabastine versus cromolyn sodium treatment of pollen-induced conjunctivitis.
Allergy, 65, 156-158.

Performance studies with antihistamines.
British Journal of Clinical Pharmacology, 6, 31-35.

Code, C.F. (1937)
The quantitative estimation of histamine in the blood.
The acute effects of acrivastine, a new antihistamine, compared with triprolidine on measures of central nervous system performance and subjective effects.
Clinical Pharmacology and Therapeutics, 38, 381-386.

The effects of acrivastine, diphenhydramine and terfenadine in combination with alcohol on human CNS performance.

Progress in automatic scoring by wrist actigraph.
Sleep Research, 19, 331.

Automatic sleep/wake identification from wrist actigraphy.
Sleep, 15, 461-469.

Histamine weal formation and absorption in man.

Coulie, P.J., Ghys, L. and Rihoux, J.P. (1991)
Cetirizine, oxatomide, ketotifen, and placebo: pharmacological evaluation of their respective antihistaminic, antipruritic and sedating effects.
Drug Investigation, 3 (5), 324-327.

Placebos and placebo effects in medicine: historical overview.
Journal of the Royal Society of Medicine, 92, 511-515.

Differentiating the effects of centrally acting drugs on arousal and memory: an event-related potential study of scopolamine, lorazepam and diphenhydramine.
Psychopharmacology, 135 (1), 27-36.

Dale, H.H. and Laidlaw, P.P. (1910)
The physiological action of iminozolylethylamine.

Danjou, P.D., Curson, C, Rosenzweig, P. Hindmarch, I. and Morselli, P. (1990)
A double blind placebo controlled study of the psychometric effects of SI850324, a new antihistaminic drug compared to terfenadine and triprolidine in healthy subjects. (abstract).

Prophylactic treatment of seasonal allergic rhinitis: a comparison of cetirizine and terfenadine.
Clinical Trials Journal, 26, 100-107.
Onset of action and efficacy of terfenadine, astemizole, cetirizine and loratadine for the
relief of symptoms of allergic rhinitis.
Annals of Allergy, Asthma and Immunology, 79 (2), 163-172.

(1997b)
Onset of action, efficacy and safety of a single dose of fexofenadine hydrochloride for
ragweed allergy using an environmental exposure unit.
Annals of Allergy, Asthma and Immunology, 79 (6), 533-540.

Cetirizine, loratadine or placebo in subjects with seasonal allergic rhinitis: effects after
controlled ragweed pollen challenge in an environmental exposure unit.
Journal of Allergy and Clinical Immunology, 101 (5), 638-645.

Effect of hydroxyzine on attention and memory.
Human Psychopharmacology, 5, 357-362.

The effects of astemizole on actual car driving and psychomotor performance.
In: O'Hanlon, J.F., and De Gier, J.J. (Eds.).
Drugs and driving.

De Roeck, J. (1992)
The sensitivity of methods used for the evaluation of drug induced daytime sedation.
Personal Communications.

Estudo comparativo entre astemizol e dexchlorfeniramina no tratamento da rinite
alergica.
A Fohla Medica, 91, 319-325.

Del Carpio, J., Kabbash, L., Turenne, Y., Prevost, M., Herbert, J., Bedard, P.M.,
Efficacy and safety of loratadine (10mg once daily), terfenadine (60mg twice daily) and
placebo in the treatment of seasonal allergic rhinitis.
Journal of Allergy and Clinical Immunology, 84, 741-746.

Effects of astemizole on psychomotor performance in healthy Thais.

Dickson, D.J. and Cruickshank, J.M. (1984)
Comparison of flunisolide nasal spray and terfenadine tablets in hay fever.
British Journal of Clinical Practice, 416-423.
Prophylactic treatment of grass-pollen induced asthma with cetirizine.
Clinical and Experimental Allergy, 20, 483-490.

Effects of a non-sedative antihistamine (loratadine) in moderate asthma.
A double blind controlled crossover trial.
Allergy, 44, 566-571.

Safety and efficacy of loratadine: a new non-sedating antihistamine in seasonal allergic rhinitis.
Annals of Allergy, 58, 407-411.

Treatment of itching in atopic eczema with antihistamines with a low sedative potential.
British Medical Journal, 298, 96.

Efficacy of loratadine versus placebo in the prophylactic treatment of seasonal allergic rhinitis.
Annals of Allergy, 73 (3), 235-239.

Lack of potentiation by cetirizine of alcohol-induced psychomotor disturbances.

Dragstedt, C.A. and Mead, F.B. (1936)
The role of histamine in canine anaphylactic shock.
Journal of Pharmacology & Experimental Therapeutics, 57, 41-426.

Brompheniramine, loratadine and placebo in allergic rhinitis: a placebo controlled comparative clinical trial.

Dose ranging comparative evaluation of cetirizine in patients with seasonal allergic rhinitis.
Annals of Allergy, Asthma and Immunology, 74 (4), 345-354.

Second generation AHs: the risk of ventricular arrhythmias.
Clinical Therapeutics, 21 (2), 281-295.
Clinical studies with terfenadine in seasonal allergic rhinitis. 
Arzneimittel Forschung, 32, 1206-1208.

Double blind placebo controlled comparison of astemizole and terfenadine in seasonal 
allergic rhinitis. 
Journal of Allergy and Clinical Immunology, 81, 228.

Side effects registered in psychological tests. 

Emonot, A., Germouty, J., Molina, C., Montane, F., Perrin-Fayolle, M., Prud’homme, A., 
Double blind multi centre study of cetirizine in grass-pollen induced asthma. 
Journal of Allergy and Clinical Immunology, 85, 145.

effects of dimethindene maleate on psychomotor performance in the oculodynamic test 
compared to placebo and loratadine. 
Drug Research, 46 (2), 887-890.

Everest, J.T., Turnbridge, R.J. and Widdop, B. (1989) 
The incidence of road accident fatalities. 
Transport and Road Research laboratory, Research Report 202, Crowthorne, Berkshire.

Human psychopharmacology of second generation antidepressants. 

Falliers C.J., Brandon, M.L., Buchman, E., Connell, J.T., Dockhorn, R., Leese, S.T., 
(1991) 
Double blind comparison of cetirizine and placebo in the treatment of allergic rhinitis. 
Annals of Allergy, 66, 257-261.

A multi-centre, double blind, placebo-controlled study investigating the anxiolytic 
efficacy of hydroxyzine in patients with generalised anxiety disorder. 
Human Psychopharmacology, 10, 181-187.

Recent clinical trials with hydroxyzine in generalised anxiety disorder. 
Acta Psychiatrica Scandinavica, 98 (suppl 393), 102-108.
Terfenadine and placebo compared in the treatment of chronic idiopathic urticaria: a
randomised double blind study.

Fink, M. and Irvin, P. (1979)
CNS effects of antihistamines, diphenhydramine and terfenadine.
Pharmakopsychitria, 12, 35-44.

Safety and efficacy of fexofenadine HCl in the treatment of chronic idiopathic urticaria.
(abstract)
Journal of Allergy and Clinical Immunology, 103 (2 part 1), S156, abs 595.

Fish, A. (1988)
Etudo comparativo multicentrique en double-aveugle de l’astemizole et de la terfenadine
dans les rhinites aperiodiques de l’adulte.
Allergie en Immunologie, 20, 373-376.

Factorial analysis of complex psychomotor performance and related skills.
Journal of Applied Psychology, 40, 96-104.

Antihistamines.

The treatment of mild to severe chronic idiopathic urticaria with astemizole: double blind
and open trials.
Journal of Allergy and Clinical Immunology, 78, 1159-1166.

The interaction between alcohol and antihistamines: clemastine.
Medical Journal of Australia, 11, 185-186.

The interaction between ethanol and antihistamines: dextchlorpheniramine.
Medical Journal of Australia, 1, 449-452.

Fraser, D.C. (1953)
The relation of an environmental variable to performance in a prolonged visual task.

Fredriksson, T., Hersle, K., Hjorth, N., Mobacken, H., Persson, T., Salde, L., Salo, O.,
Schmidt, H. and Thomsen, K. (1986)
Terfenadine in chronic urticaria: a comparison with clemastine and placebo.
Cutis, August, 128-129.
The effects of time of day, age and anxiety on a choice reaction task.
In: Hindmarch, I, Aufdembrinke, B., and Ott, H. (Eds.)
Psychopharmacology and Reaction Time. pp 103-114.
John Wiley & Sons, Chichester, UK.

The effects of nefazodone, imipramine and placebo alone and combined with alcohol in normal subjects.
International Clinical Psychopharmacology, 8, 13-20.

Freyd, M. (1923)
The graphic rating scale.
Journal of Educational Psychology, 14, 83-102.

A multicentre study of loratadine, clemastine and placebo in patients with perennial allergic rhinitis.
Allergy, 45, 254-261.

Astemizole in the treatment of seasonal allergic rhinitis: a double blind comparison with clemastine in patients sensitive to tree and grass pollen. Special reference to side effects registered in psychological tests.

A comparison of topical levocabastine and sodium cromoglycate in the treatment of pollen-provoked allergic conjunctivitis.
Clinical and Experimental Allergy, 23 (5), 406-409.

Fudge, J.L., Perry, P.J., Garvey, M.J. and Kelly, M.W. (1990)
A comparison of the effects of fluoxetine and trazadone on the cognitive functioning of depressed outpatients.
Journal of Affective Disorders, 18, 275-280.

Ineffectiveness of oral terfenadine in natural colds: evidence against histamine as a mediator of common cold symptoms.

The influence of antihistamines on human performance.

Terfenadine and clemastine in the treatment of acute pollenotic rhinitis.
Comparison of the suppressive effect of astemizole, terfenadine, and hydroxyzine on histamine-induced wheals and flares in humans.
Journal of Allergy and Clinical Immunology, 77 (2), 335-340.

The relative antihistaminic effects of hydroxyzine and cetirizine.
Clinical Pharmacology and Therapeutics, 42 (3), 265-272.

Antihistamines, drowsiness and psychomotor impairment: CNS effects of cetirizine.
Annals of Allergy, 59, 53-57.

Gengo, F.M., Gabos, C. and Mechtler, L. (1990)
Quantitative effects of cetirizine and diphenhydramine on mental performance measured using an automobile driving simulator.
Annals of Allergy, 64, 520-526.

The pharmacodynamics of diphenhydramine-induced drowsiness and changes in mental performance.
Clinical Pharmacology Therapeutics, 45 (1), 15-21.

French multi centre study to evaluate the efficacy and safety of acrivastine as compared with terfenadine in seasonal allergic rhinitis.
Journal of International Medical Research, 17, 47-53.

Dermatologica, 169, 179-183.

Double blind comparison of astemizole, terfenadine and placebo in hay fever with special regard to onset of action.
Journal of International Medical Research, 13, 102-108.

Double blind placebo controlled comparison of cetirizine and terfenadine in chronic idiopathic urticaria.
Acta Therapeutica, 15, 77-86.

Objective antihistamine side effects are mitigated by evening dosing of hydroxyzine.
Annals of Allergy, 67, 448-454.
Prolongation of simple and choice reaction times in double blind comparison of twice 
daily hydroxyzine versus terfenadine. 
Journal of Allergy and Clinical Immunology, 83 (4), 316-322.  

Pharmacokinetic overview of oral second generation H₁ antihistamines. 

Retest reliability and construct validity of critical flicker fusion frequency. 
Pharmacopsychiatry, 15 (suppl 1), n 24-28.  

Grant, J.A., Bernstein, D.I., Buckley, E.C., Chu, T., Fox, R.G., Rocklin, R.E., 
Double blind comparison of terfenadine, chlorpheniramine and placebo in the treatment 
of chronic idiopathic urticaria. 
Journal of Allergy and Clinical Immunology, 81, 574-579.  

A double blind, single dose, crossover comparison of cetirizine, ebastine, epinastine, 
fexofenadine, terfenadine and loratadine versus placebo: suppression of histamine-
induced weal and flare response for 24 hours in healthy male subjects. 
Allergy, 54 (7), 700-707.  

Astemizole suspension in the maintenance treatment of pediatric hay fever: a comparison 
with terfenadine suspension. 
Pharmatherapeutica, 4, 642-647.  

Loratadine pseudoephedrine combination versus placebo in patients with seasonal 
allergic rhinitis. 
Annals of Allergy, 63, 317-321.  

CFF and assessment of pharmacodynamics: role and relationship to psychometric, EEG, 
and pharmacokinetic variables. 
Pharmacopsychiatria, 15, Suppl 1, 29-35.  

Grunstrom, R.T., Holmberg, G. and Hansen, T. (1978) 
Degree of sedation obtained with various doses of diazepam and nitrazepam. 

Grunstrom, R.T., Holmberg, G., Ledermann, H. and Livstedt, B. (1977) 
Sedative properties of doxepin in comparison with diazepam. 
Psychopharmacology, 54, 165-169.


Hayes, M.H. and Patterson, D.G. (1921) Experimental development of the graphic rating method. Psychological Bulletin, 18, 98.
Some central and peripheral effects of meclastine, a new antihistaminic drug, in man.
Clinical Pharmacology, 11, 112-119.

Multicentre double blind comparison of terfenadine once daily versus twice daily in patients with hay fever.
Journal of International Medical Research, 15, 212-223.

Hindmarch, I. (1975)
1,4-benzodiazepine, temazepam: its effects on some psychological parameters of sleep and behaviour.
Arzneimittel Forschung, 25 (11), 1836-1839

Hindmarch, I. (1976)
The effects of subchronic administration of an antihistamine, clemastine, on tests of car driving ability and psychomotor performance.
Current Medical Research and Opinion, 4, 197-206.

Hindmarch, I. (1979)
A preliminary study of the effects of repeated doses of clobazam on aspects of performance, arousal and behaviour in a group of anxiety rated volunteers.

Hindmarch, I. (1980)
Psychomotor function and psychoactive drugs.
British Journal of Clinical Pharmacology, 10, 189-209.

Measuring the effects of psychoactive drugs on higher brain activity.
In: Burrows, G.D. and Werry, J.S. (eds.)
Advances in Human Psychopharmacology, Volume 2.

Critical flicker fusion frequency (CFF): The effects of psychotropic compounds.
Pharmacopsychiatria, 15, Suppl 1, 44-48.

Hindmarch, I. (1983)
The subjective evaluation of sleep.
In: Medicine Publishing Foundation Symposium Series, No 10.

Hindmarch, I. (1986)
The effects of psychoactive drugs on car handling and related psychomotor ability; a review.
In: O’Hanlon, J.F., and de Gier, J.J. (Eds.). Drugs and driving.
Taylor & Francis, London, UK.
Hindmarch, I. (1987)
Three antidepressants with and without alcohol, compared with placebo on tests of psychomotor ability and car driving.
Human Psychopharmacology, 2, 177-183

The psychopharmacological approach: effects of psychotropic drugs on car handling.
International Clinical Psychopharmacology, 3 (1), 73-79.

Hindmarch, I. (1990)
Human psychopharmacological differences between benzodiazepines.

Hindmarch, I. (1994)
Neuroleptic-induced deficit syndrome: behavioural toxicity of neuroleptics in amn.

Hindmarch, I. (1999)
It's all in the mind: Measuring somnolence and CNS drug side effects.
Human Psychopharmacology: Clinical & experimental, 13, 385-387.

Psychopharmacology and reaction time.
John Wiley and Sons, Chichester, UK.

Hindmarch, I. and Bhatti, J.Z. (1987)
Psychomotor effects of astemizole and chlorpheniramine, alone and in combination with alcohol.
International Clinical Psychopharmacology, 2, 117-119.

The anatomy of a clinical trial.
Human Psychopharmacology: Clinical and Experimental, 14, 103-108.

A placebo controlled assessment of mequitazine and astemizole in tests of psychomotor ability.

Assessing the residual effects of hypnotics.
Acta Psychiatraca Belgica, 94, 88-95.
The effects of clobazam and lorazepam on aspects of psychomotor performance and car handling ability.
British Journal of Clinical Pharmacology, 10 (2), 145-150.

Effects of paroxetine on cognitive function in depressed patients, volunteers and elderly volunteers.
Medical Science Research, 22, 669-670.

The effects of alcohol and other drugs on psychomotor performance and cognitive function.
Alcohol and Alcoholism, 26 (1), 71-79.

Hindmarch, I. and Parrott, A.C. (1978a)
A repeated dose comparison of the side effects of five antihistamines on objective assessments of psychomotor performance, central nervous system arousal and subjective appraisals of sleep and early morning behaviour.
Drug Research, 28 (1), 483-487.

Hindmarch, I. and Parrott, A.C. (1978b)
The effect of a subchronic administration of three dose levels of a 1,5-benzodiazepine derivative, clobazam, on subjective aspects of sleep and assessments of psychomotor performance the morning following night time administration.
Arzneimittel Forschung, 28 (II), 2169-2172.

The effects of black tea and other beverages on aspects of cognitive and psychomotor performance.
Psychopharmacology, 139, 230-238.

Psychometric aspects of antihistamines.
Allergy, 50, 48-54.

Models to assess sedative properties of antihistamines.
Clinical and Experimental Allergy, 29 (S3), 133-142.

A double blind, placebo controlled investigation of the effects of fexofenadine, loratadine and promethazine on cognitive and psychomotor function.

The effects of midazolam in conjunction with alcohol on sleep, psychomotor performance and car driving ability.
The effects of antidepressants taken with and without alcohol on information processing, psychomotor performance and car driving ability.
In: O’Hanlon, J.F., and de Gier, J.J. (Eds.)
Drugs and Driving. London: Taylor and Francis.

The effects of zimeldine and amitriptyline on car driving and psychomotor performance.
Acta Psychiatrica Scandinavica, 68 (suppl 308), 141-146.

A comparison of the psychometric effects of remixipride with those of haloperidol, thioridazine and lorazepam in healthy volunteers.
Human Psychopharmacology, 9, 43-49.

Hinton, P.R. (1995)
Analysing frequency data: chi-square.

Hoechst Marion Roussel (1999)
Telfast 120mg and 180mg.
ABPI compendium of data sheets and summaries of product characteristics.
Datapharm publications limited, London, UK.

CNS Drugs, 9 (2), 85-98.

Antihistamines in the treatment of asthma.
Clinical Review in Allergy, 12, 65-78.

Astemizole in seasonal allergic rhinitis and conjunctivitis.
In: Astemizole: a new, non-sedative, long-acting H1 antagonist.

Holmberg, G. (1981)
Critical Flicker Fusion (CFF) test for the sedative effects of antidepressants: recent advances in the treatment of depression.
Acta Psychiatrica Scandinavica, 63 (Suppl 290), 289-301.

Placebo controlled comparison of the acute effects of ebastine and clemastine on performance and EEG.
A multicentre study of loratadine, terfenadine and placebo in patients with seasonal allergic rhinitis.
Arzneimittel Forschung, 38, 124-128.

Efficacy and safety relative to placebo of an oral formulation of cetirizine and sustained release pseudoephedrine in the management of nasal congestion.
Allergy, 53 (9), 849-856.

Hosinger, R.W. and Thomsen, R.J. (1990)
Prolonged benefit in the treatment of chronic idiopathic urticaria with astemizole.
Annals of Allergy, 65, 194-200.

Determining the safety and efficacy of antihistamines.
Presented at the 17th Congress of the European Academy of Allergology and Clinical Immunology, Birmingham, UK.

Astemizole, a potent H1 histamine receptor antagonist: effect in allergic rhinoconjunctivitis, on antigen and antihistamine-induced skin weal responses and relationship to serum levels.

Comparative trial of the two non-sedative H1 antihistamines, terfenadine and astemizole for hay fever.
Thorax, 39, 668-672.

Hughes, F.W. and Forney, R.B. (1964)
Comparative effects of three antihistaminics and ethanol on mental and motor performance.
Clinical Pharmacology and Therapeutics, 5, 414-421.

Inhibitory activity of terfenadine on histamine induced skin weals in man.
European Journal of Clinical Pharmacology, 12, 195-199.

Irander, K., Odkvist, L.M. and Ohlander, B. (1990)
Treatment of hay fever with loratadine, a new non-sedating antihistamine.
Allergy, 45, 86-91.

A novel class (H3) of histamine receptor on perivascular nerve terminals.
Nature, 327, 117-123
Routeplanning en geleiding.

Sedating drugs and automobile accidents leading to hospitalisation.

Treatment of chronic urticaria with cetirizine dihydrochloride, a non-sedating antihistamine.

Acrivastine versus clemastine in the treatment of chronic idiopathic urticaria. A double blind placebo controlled study.

Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis.
Journal of Allergy and Clinical Immunology, 83, 627-633.

Efficacy of continuous treatment with astemizole and terfenadine in ragweed pollen-induced rhinoconjunctivitis.
Journal of Allergy and Clinical Immunology, 82, 670-675.

A double blind trial of terfenadine and placebo in hay fever using a substitution technique for non-responders.
Journal of International Medical Research, 8, 404-407.

Kaliner, M.A. (1992)
Non-sedating antihistamines: pharmacology, clinical efficacy and adverse effects.
American Family Physician, 45 (3), 1337-1342.

Kalivas, J., Breneman, D., Tharp, M., Bruce, S. and Bigby, M. (1990)
Urticaria: Clinical efficacy of cetirizine in comparison with hydroxyzine and placebo.
Journal of Allergy and Clinical Immunology, 86, 1014-1018.

Effects of loratadine in suppression of histamine induced skin weals.
Annals of Allergy, 60, 505-507.

CogScreen (Aeromedical Eds.), Professional Manual.
Odessa, FL: Psychological Assessment Resources, Inc.
Self reported sedation doesn't predict impaired CNS functioning after dose of sedating antihistamine. (abstract)  
Journal of Allergy and Clinical Immunology, 103, 975, S254.

Loratadine: a non-sedating antihistamine. Review of its effects on cognition, psychomotor performance, mood and sedation.  
Clinical and Experimental Allergy, 29 (S3), 147-150.

Sedating effects of AM/PM antihistamine dosing with evening chlorpheniramine and morning terfenadine.  
American Journal of Man Care, 3, 1843-1848.

Multicentre, double blind placebo controlled, trial of terfenadine in seasonal allergic rhinitis and conjunctivitis.  
Annals of Allergy, 54, 502-509.

A multicentre, open study of the non-sedating antihistamine, terfenadine, in the maintenance therapy of seasonal allergic rhinitis.  
Annals of Allergy, 60 (4), 349-54.

Kennedy, R.S., Bittner, A.C. and Jones, M.B. (1981)  
Video game and conventional tracking.  
Perceptual Motor Skills, 53, 310.

The psychomotor and cognitive effects of a new antihistamine, mizolastine, compared to terfenadine, triprolidine and placebo in healthy volunteers.  
European Journal of Clinical Pharmacology, 47, 331-335.

Correlation between doses of oxazepam and their effects on performance of a standardised test battery.  

The effects of reboxetine and amitriptyline with and without alcohol on cognitive function and psychomotor performance.  

Separate and combined effects of the social drugs on psychomotor performance.  
Psychopharmacology, 104 (1), 113-119.
Kiehn, R. (1986)
Heuschnupfen: Tritoqualin und astemizol. Eine randomisierte, kontrollierte
vergleichsstudie zweier medikamente.

Comparison of cetirizine and terfenadine in the treatment of chronic idiopathic urticaria.
Annals of Allergy, 65 (6), 498-500.

Kilminster, S.G. (1991)
Age related memory impairment: a longitudinal and cross-sectional comparison.
In: Hindmarch H, Hippus, H and Wilcock, G (Eds.).
Dementia: Molecules, Methods and Measures. John Wiley & Sons, Chichester, UK.

Comparative efficacy of cetirizine and terfenadine in the treatment of chronic idiopathic
urticaria.
Acta Therapeutica, 15, 65-75.

Brompheniramine, terfenadine and placebo in allergic rhinitis.
Annals of Allergy, Asthma and Immunology, 77 (5), 365-370.

Knight, A. (1985)
Astemizole, a new non-sedating antihistamine for hay fever.
Journal of Otolaryngology, 14, 85-88.

Knight, A., Drouin, M.A., Yang, W.H., Alexander, M., Deal Carpio, J. and Arnott, W.S.
(1991)
Clinical evaluation of the efficacy and safety of norebastine, a new H1 antagonist, in
seasonal allergic rhinitis: a placebo controlled, dose response study.
Journal of Allergy and Clinical Immunology, 88 (6), 926-934.

Acrivastine versus hydroxyzine in the treatment of cholinergic urticaria.
Dermato-Venereologica, 68, 541-544.

Lack of effects of astemizole on vestibular ocular reflex, motion sickness and cognitive
performance in man.
Aviation, Space and Environmental Medicine, Dec, 1171-1174.

Cetirizine inhibits delayed pressure urticaria.
Annals of Allergy, 65 (6), 520-522.
Repeated measures on a choice reaction time task.  
Research Report, NBDL - 82R006, New Orleans, Naval Biodynamics Laboratory.

Mode of action of H\textsubscript{1} antihistamines in itch.  
British Journal of Dermatology, 109 (S24), 30.

The effect of terfenadine on dermographic wealing.  
British Journal of Dermatology, 110, 73-79.

Some clinical pharmacological studies with terfenadine, a new antihistamine drug.  
British Journal of Clinical Pharmacology, 6, 25-29.

Comparison of cetirizine with astemizole in the treatment of perennial allergic rhinitis  
and study of the concomitant effect on histamine and allergen-induced weal responses.  
Annals of Allergy, 65 (5), 401-405.

A multi-centre double-blind comparison of hydroxyzine, buspirone and placebo in  
patients with generalised anxiety disorder.  
Psychopharmacology, 139 (4), 402-406.

The effects of nitrazepam on manual skill, grip strength and reaction time with special  
reference to subjective evaluation of effects on sleep.  
Acta Pharmacology and Toxicology, 42, 130-134.

Landis, C. (1953)  
An annotated bibliography of flicker fusion phenomena (covering the period 1740-1952).  
Ann Arbor, Armed Forces National Research Council and University of Michigan.

Laugier, P. and Orusco, M. (1978)  
Comparative trial of an antihistamine, mequitazine and placebo.  
Current Medical Research and Opinion, 5, 371-375.

Effect of mequitazine, a non-sedative antihistamine on brain H\textsubscript{1} receptors.  
Life Sciences, 29 (6), 547-552.

Levander, S.E. (1982)  
Computerised CFF: reliability and validity of two psychophysical techniques.  
Pharmacopsychiatrica, 15 (suppl 1), 2-33.
Peripheral antihistamine and central sedative effects of three H₁ receptor antagonists.
European Journal of Clinical Pharmacology, 28, 523-529.

Peripheral antihistamine and central sedative effects of a single and continuous dosing of

cetirizine and hydroxyzine.

A comparison of acrivastine versus clemastine and placebo in the treatment of patients
with chronic idiopathic urticaria.
Journal of International Medical Research, 17, 228-248.

Group comparative trial of cromolyn sodium and terfenadine in the treatment of seasonal
allergic rhinitis.
Annals of Allergy, 58, 28-32.

Linnoila, M. (1973)
Effects of antihistamines, chlormezanone, and alcohol on psychomotor skills related to
driving.
European Journal of Clinical Pharmacology, 5, 247-254

Lockey, R.F., Widlitz, M.D., Mitchell, D.Q., Lumry, W., Dockhorn, R., Woehler, T. and
Comparative study of cetirizine and terfenadine versus placebo in the symptomatic
treatment of seasonal allergic rhinitis.
Annals of Allergy, Asthma and Immunology, 76 (5), 448-454.

Children with allergies. Terfenadine versus placebo.
The Practitioner, 227, 1313-1315.

Effect in patients exposed to grass pollen.

Safety of fexofenadine HCl in children treated for seasonal allergic rhinitis. (abstract)
Journal of Allergy and Clinical Immunology, 103 (2 part 1), S254, abs 972.

Longo, G. (1990)
Loratadina and desclorfeniramina nel trattamento della rhinitis allergica perenne in
pazienti pediatrici.
Minerva Pediatrica, 42, 179-183.

Central nervous system effects of antihistamines on evoked potentials.
Annals of Allergy, 63 (II), 604-608.
Lundberg, P.K. (1980)  
Assessment of drugs’ side effects: Visual analogue scale versus checklist format.  
Perceptual and Motor Skills, 50, 1067-1073.

Comparison of the effects of azatadine maleate and terfenadine on human performance.  
Pharmatherapeutica, 3 (6), 370-375.

Evaluation of a bedtime dose of a combination antihistamine/decongestant product on antigen challenge the next morning.  
Laryngoscope, 102 (3), 330-334.

In vivo and in vitro evaluation for four antihistamines (astemizole, azatadine, mequitazine and terfenadine).  
Allergologia et Immunopathologica, 17, 85-93.

Malling, H.J. (1987)  
Quantitative skin prick testing.  
Allergy, 42, 196-204.

Astemizole in the treatment of hay fever.  
Allergy, 38, 227-231.

Non sedating histamine receptor antagonists.  
Clinical Pharmacology, 8, 331-344.

Efficacy and safety of cetirizine in perennial allergic rhinitis.  
Annals of Allergy, 68 (4), 348-353.

Diazepam effects on the performance of healthy subjects are not enhanced by treatment with the antihistamine, ebastine.  

Lack of pharmacodynamic and pharmacokinetic interactions of the antihistamine ebastine with ethanol in healthy subjects.  
European Journal of Clinical Immunology, 43, 179-184.
Acute and sub acute actions on human performance and interactions with diazepam of
temelastine and diphenhydramine.

McNemar, O.W. (1951)
Ordering of individuals in critical flicker frequency under different measurement
conditions.

Terfenadine: An updated review of its pharmacological properties and therapeutic
efficacy.
Drugs, 39 (4), 552-574.

Differential cognitive effects of terfenadine and chlorpheniramine.
Journal of Allergy and Clinical Immunology, 84 (3), 322-325.

Melillo, G., D'Amato, G., Zanussi, C., Ortolani, C., Pastorello, E., Loy, M., Di Tucci, A.,
A multicentre controlled trial of terfenadine, dexchlorpheniramine and placebo in allergic
rhinitis.
Drug Research, 32, 1202-1203.

Meltzer, E.O. (1990)
Performance effects of antihistamines.
Journal Allergy and Clinical Immunology, 86 (4, pt II), 613-619.

Comparative safety of H1 antihistamines.
Annals of Allergy, 67, 625-633.

Comparative outdoor study of the efficacy, onset and duration of action and safety of
cetirizine, loratadine and placebo for seasonal allergic rhinitis.
Journal of Allergy and Clinical Immunology, 97 (2), 617-626.

Adverse effects of H1 receptor antagonists in the central nervous system.
In: Simons (Eds.). Histamine and H1 receptor antagonists in allergic disease.
New York: Marcel Dekker, Increase., 357-81.

Michel, L., De Vos, C. and Dubertret, L. (1990)
Cetirizine effects on the cutaneous allergic reaction in humans.
Annals of Allergy, 65 (6), 512-516.
Miller, K. and Standen, P.J. (1982)
Differences in performance impairment due to brompheniramine maleate as a function of
the sustained release system.
British Journal of Clinical Pharmacology, 14, 49-55.

Efficacy and tolerance of terfenadine suspension in children with allergic rhinitis.

Moller, C. and Blychert, L.O. (1990)
Levocabastine eye drops in comparison with cromoglycate in the treatment of
conjunctivitis in children with birch pollinosis.
Paediatric Allergy Immunology, 1, 87-89.

Effects of promethazine hydrochloride on hand-eye co-ordination.

The role of antihistamines in the treatment of chronic urticaria.
Journal of Allergy & Clinical Immunology, 86(4), 662-665.

Monroe, E.W., Bernstein, D.I., Fox, R.W., Grabiec, S.V., Honsinger, R.W., Kalivas, J.T.,
Relative efficacy and safety of loratadine, hydroxyzine and placebo in chronic idiopathic
urticaria.
Arzneimittel Forschung, 42 (II), 1119-1121.

Comparison of cimetidine and diphenhydramine in the treatment of chronic urticaria.
Annals of Emergency Medicine, 19, 12-15.

Moscato, G. and Fasani, F. (1988)
Trattamento dell'occulorinite allergica stagionale conclusion astemizolo: un confronto in
doppio ciego conclusion la terfenadine.
Folla Allergologica Immunologica Clinica, 35, 409-417.

Effects of terfenadine and diphenhydramine alone or in combination with diazepam or
alcohol on psychomotor performance and subjective feelings.

Antihistamines and reactivity.
Drug Research, 33, 262-265.

Effects of terfenadine, diphenhydramine and placebo on skilled performance.
Cutis, 42, 14-16.
Wrist-actigraphic estimation of sleep time.
Sleep, 3, 83-92.

The effects of terfenadine versus hydroxyzine and placebo on simple and choice reaction time. (Abstract).
Journal of Allergy and Clinical Immunology, 79: 189.

Comparative trial of two dose regimens of terfenadine in patients with hay fever.
Journal of International Medical Research, 12, 333-337.

evaluation of antihistamine-related daytime sleepiness.
Allergy, 47, 532-534.

Comparison of efficacy and safety of cetirizine and ebastine in patients with perennial allergic rhinitis.
Annals of Allergy, Asthma and Immunology, 80 (5), 399-403.

A double blind randomised evaluation of astemizole in comparison with placebo in the treatment of seasonal allergic rhinitis.
Journal of Allergy and Clinical Immunology, 75, 166.

Comparison of the new antihistamine, acrivastine (BW 825C) versus cyproheptadine in the treatment of idiopathic cold urticaria.
Dermatologica, 177, 98-103.

Netter, K.J. and Bodenschatz, K. (1967)
Inhibition of histamine-N-ethylation by some antihistamines.
Biochemical Pharmacology, 16, 1627-1631.

Levocabastine compared with sodium cromoglycate eyedrops in children with both birch and grass pollen allergy.
Paediatric Allergy and Immunology, 3, 39-42.

Nicholson, A.N. (1979)
Effects of the antihistamines, brompheniramine maleate and triprolidine hydrochloride, on performance in man.
British Journal of Clinical Pharmacology, 8, 321-324.

Histaminergic systems and sleep.
Neuropharmacology, 24 (3), 245-250.
Alertness and performance in man with enantiomers of chlorpheniramine and
dimethindene.
British Journal of Clinical Pharmacology, 734-735 (get volume)

Antihistamines and visual function: studies on dynamic visual acuity and the pupillary
response to light.
British Journal of Clinical Pharmacology, 14, 683-690.

Performance studies with the H<sub>1</sub> histamine receptor antagonists, astemizole and
terfenadine.

The H<sub>1</sub> antagonist mequitazine: Studies on performance and visual function.

Antihistamines: Impaired performance and the tendency to sleep.
European Journal of Clinical Pharmacology, 30, 27.

Central effects of H<sub>1</sub>-antihistamine, cetirizine.
Aviation, Space and Environmental Medicine, 69 (2), 166-171.

Drugs affecting the inner ear: a review of their clinical efficacy, mechanisms of action,
toxicity and place in therapy.
Drugs, 36, 754-72.

Treatment of allergic rhinitis: fexofenadine versus loratadine. (abstract)
Annals of Allergy, Asthma and Immunology, 80 (1), abs 40.

Odelram, H., Bjorksten, B., Af Klercker, T., Rimas, M., Kjellman, N.I.M. and Blychert,
Topical levocabastine versus sodium cromoglycate in allergic conjunctivitis.
Allergy, 44, 432-436.

Oei, H.D. (1988)
Double blind comparison of loratadine, astemizole and placebo in hay fever with special
regard to onset of action.
Annals of Allergy, 61, 436-439.
Boredom: practical consequences and a theory.
Acta Psychologica, 49, 53-82.

Antihistamines and driving safety.

Terfenadine and brompheniramine maleate in urticaria dermographism.
Dermatologica, 173, 5-8.

The effects of practice on choice reaction time and critical flicker fusion threshold.
Human Psychopharmacology, 12, 65-70.

Critical Flicker Fusion Thresholds and their relationships to other measures.
Pharmacopsychiatry, 15 (suppl 1), 39-43.

Parrott, A.C. (1991a)

Parrott, A.C. (1991b)
Performance tests in human psychopharmacology (2): content validity, criterion validity and face validity.
Human Psychopharmacology, 6, 91-98.

Parrott, A.C. (1991c)
Performance tests in human psychopharmacology (3): construct validity and test interpretation.
Human Psychopharmacology, 6, 197-207.

Factor analysis of a sleep questionnaire.
Psychological Medicine, 8, 325-329.

Parrott, A.C. and Hindmarch, I. (1980a)
The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations: a review.

Promethazine, scopolamine, and cinnarizine: comparative time course of psychological performance effects.
Psychopharmacology, 92, 513-519.
The clinical safety of H₁ receptor antagonists.
Allergy, 51, 666-675.

Antihistaminic treatment of allergic rhinitis: a double blind study with terfenadine versus dextchlorpheniramine.
Pharmatherapeutica, 5, 69-75.

Journal of Dermatology Treatment, 9, 1430149.

Paul, E. and Bodeker, R.H. (1986)
Treatment of chronic urticaria with terfenadine and ranitidine: a randomised double blind study in 45 patients.

Comparative study of astemizole and terfenadine in the treatment of chronic idiopathic urticaria. A randomised double blind study of 40 patients.
Annals of Allergy, 62, 318-320.

Effects of mizolastine, a new antihistamine on psychomotor performance and memory in elderly subjects.

A comparison of central and peripheral effects of cetirizine and loratadine.
The Journal of International Medical Research, 19 (4), 289-295.

Comparison of the central and peripheral effects of cetirizine and terfenadine.

A comparison of triprolidine and clemastine on histamine antagonism and performance tests in man: implications for the mechanism of drug-induced drowsiness.
European Journal of Pharmacology, 8, 455-463.
Antihistamines: the old and the new.
American Family Physician, 52 (2), 593-600.

Tratamiento de la rinitis alergica del niño. Conclusión: un nuevo antihistamínico.
Alergia, 32, 45-49.

Current medical management of rhinitis in flying personnel.
Advances in Therapy, 10 (4), 159-166.

A double blind evaluation of topical levocabastine, a new specific antihistamine in patients with allergic conjunctivitis.
Allergy, 40, 491-496.

European Academy of Allergology and Clinical Immunology, Rhodes, Greece.

Subjective and behavioural effects of diphenhydramine, lorazepam and methocarbamol.

Acrivastine, terfenadine and diphenhydramine effects on driving performance as a function of dose and time after dosing.
European Journal of Clinical Pharmacology, 47, 261-266.

Effects of moclobemide and mianserin on highway driving, psychoperformance and subjective parameters, relative to placebo.
Psychopharmacology, 106, 562-567.

Effects of loratadine and cetirizine on actual car driving and psychometric test performance, and EEG during driving.

Chronopharmacological study of antihistamines in man with special references to terfenadine.
European Journal of Clinical Pharmacology, 14, 245-252.

Multicentre, cross-over study of the efficacy and tolerability of terfenadine 120mg versus cetirizine 10mg in perennial allergic rhinitis.
Annals of Allergy, 67 (4), 416-420.
Repp, V. (1985)
Ein vergleich von astemizol und terfenadin in der enhaltungs therapie des heuschnupfens.
Zeitschrift für Hautkrankheiten, 60, 43-45.

Cutaneous reactivity to mosquito bites: effect of cetirizine and development of anti-mosquito antibodies.
Clinical and Experimental Allergy, 21 (5), 617-622.

Rice, V.J. and Snyder, H.A. (1993a)
The effects of Benadryl and Hismanal on psychomotor performance and perceived performance.
Aviation, Space and Environmental Medicine, Aug, 726-733.

Rice, V.J. and Snyder, H.A. (1993b)
The effects of Benadryl and Hismanal on mood, physiological measures, antihistamine detection and subjective symptoms.
Aviation, Space and Environmental Medicine, Aug, 717-725.

Astemizole: A review of its pharmacodynamic properties and therapeutic efficacy.
Drugs, 28, 38-61.

How many people think they have hay fever and what they do about it.
British Journal General Practice, 42, 284-286.

Higher doses of terfenadine and loratadine: acute and subchronic effects on psychomotor and actual driving performance.
IGVG 90-08, March.

Cetirizine 10mg and 20mg impair psychomotor performance.
Clinical and Experimental Allergy, 20, 97.

The clinical efficacy of H1 antihistamines in urticaria and rhinitis.
Journal of Allergy and Clinical Immunology, 102 (2), 333-334.

Comparative study of the peripheral and central effects of terfenadine and cetirizine 2HCl.
Annals of Allergy, 59, 235-238.


Lack of behavioural toxicity of mizolastine: a review of the clinical pharmacology studies.
Clinical and Experimental Allergy, 29 (S3), 156-162.

Sedative effects of antihistamines.
Journal of Allergy and Clinical Immunology, 80 (1), 94-98.

Actigraphically based automatic bedtime sleep-wake scoring: validity and clinical applications.
Journal of Ambulatory Monitoring, 2, 209-216.

Activity-based sleep-wake identification: an empirical test of methodological issues.
Sleep 17, 201-207.

Salisbury, J., Bor, S. and Blair, C. (1987)
A double blind placebo controlled study of terfenadine in the treatment of chronic idiopathic urticaria.
The British Journal of Clinical Practice, 41, 859-861.

A comparison of acrivastine versus hydroxyzine and placebo in the treatment of chronic idiopathic urticaria.
Journal of International Medical Research, 17, 18B-21B.

Salomonsson, P. (1988)
Efficacy of an oral antihistamine, astemizole as compared to a nasal steroid in hay fever.
Allergy, 43, 214-218.

Retentissement sur le fonctions cognitives de deux traitements anxiolytiques chez des patients souffrant d’anxiete generalisee.
Encephale, 21, 147-153.

Pharmacokinetics and pharmacodynamics of diphenhydramine 25mg in young and elderly volunteers.
Journal of Clinical Pharmacology, 38, 603-609.

Suppression of seasonal allergic rhinitis symptoms with daily hydroxyzine.
Journal of Allergy and Clinical Immunology, 63, 129-133.


Schweitzer, P.K., Muelbach, M.J. and Walsh, J.K. (1994) Sleepiness and performance during three day administration of cetirizine or diphenhydramine. Journal of Allergy and Clinical Immunology, 94 (4), 716-724.


Shamsi, Z. and Hindmarch, I. (1999b)
The effects of single and repeated administration of ebastine on cognition and psychomotor performance in comparison to triprolidine and placebo in healthy volunteers.
Drugs under Experimental and Clinical Research, (Under Review).

Shamsi, Z. and Hindmarch, I. (1999c)
The effects of hydroxyzine and lorazepam on cognitive function and sleep in patients with generalised anxiety disorder.
Neuropsychobiology, (Under Review).

A comparative study of clemastine and chlorpheniramine maleate in the treatment of hay fever.
Current Medical Research and Opinion, 6, 245-249.

Sherwood, N. (1993)
Effects of nicotine on human psychomotor performance.
Human Psychopharmacology, 8, 155-184.

A comparison of five commonly prescribed antidepressants with particular reference to their behavioural toxicity.
Human Psychopharmacology, 8, 417-422.

The reliability, validity and pharmacosensitivity of four psychomotor tests.
In: Human Psychopharmacology, Methods and Measures, Volume 4, Edited by Hindmarch I. & Stonier P.D. John Wiley and Sons, Chichester, UK.

Current status and future prospects for anxiolytic drug therapy.
Primary Care Psychiatry, 4, 157-167.

H1 receptor antagonists: clinical pharmacology and therapeutics.
Journal Allergy and Clinical Immunology, 84, 835-861.

New H1 receptor antagonists: Clinical Pharmacology
Clinical and Experimental Allergy, 20 (2), 19-24.
The clinical pharmacology of fexofenadine.
Journal of Allergy and Clinical Immunology, 98 (6-1), 1062-1064

Evolution of H1 receptor antagonist treatment.
Annals of Allergy, 71, 282-287.
A new classification of $H_1$ receptor antagonists.
Allergy, 50, 7-11.

The eternal triangle: benefit, risk and cost of therapeutic agents.
Annals of Allergy, Asthma and Immunology, 77, 337-339.

Simons, F.E., Fraser, T.G., Maher, J., Pillay, N. and Simons, K.J. (1999)
Central nervous system effects of $H_1$ receptor antagonists in the elderly.
Annals of Allergy, Asthma and Immunology, 82 (2), 157-160.

Simons, F.E.R., Fraser, T.G., Reggin, J.D. and Simons, K.J. (1995)
Individual differences in central nervous system response to $H_1$-receptor antagonists.
Annals of Allergy, Asthma and Immunology 75 (6 pt1), 507-514.

Simons, F.E.R., Fraser, T.G., Reggin, J.D. and Simons, K.J. (1996)
Comparison of the CNS effects produced by six $H_1$-receptor antagonists.
Clinical and Experimental Allergy, 26 (9), 1092-7.

A double blind, crossover, single dose comparison of cetirizine, terfenadine, loratadine,
astemizole, and chlorpheniramine versus placebo: suppressive effects on histamine
induced wheals and flares during 24 hours in normal subjects.
Journal of Allergy and Clinical Immunology, 86(4), 540-547.

New $H_1$ receptor antagonists: a review.
American Journal of Rhinology, 2, 21-25.

Second generation $H_1$ receptor antagonists.
Annals of Allergy, 66, 5-21.

Peripheral $H_1$ blockade effect of fexofenadine.
Annals of Allergy, Asthma and Immunology, 79, 530-532.

An investigation of the $H_1$ receptor antagonist triprolidine: pharmacokinetics and
antihistaminic effects.
Journal of Allergy and Clinical Immunology, 77 (2), 326-330.

Simonson, E. and Brozek, J. (1952)
Flicker fusion frequency: background and applications.
Physiological Reviews, 32, 340-378.
Skassa-Brociek, W., Bosquet, J. and Montes, F. (1988)
Double blind placebo controlled study of loratadine, mequitazine and placebo in the
symptomatic treatment of seasonal allergic rhinitis.
Journal of Allergy and Clinical Immunology, 81, 725-730.

A comparative study of the sedative effects of diphenhydramine, astemizole, and
placebo.
Presented at: The Annual Meeting of the American Academy of Allergy and
Immunology, March 1984

Critical flicker fusion and psychotropic drugs in normal human subjects: a review.
Psychopharmacology, 47, 175-182.

Sohoel, P., Freng, B.A., Kramer, J., Poppe, S., Rebo, R., Korsrud, F.R., Garud, O.,
Topical levocabastine compared with orally administered terfenadine for the prophylaxis
and treatment of seasonal rhinoconjunctivitis.
Journal of Allergy and Clinical Immunology, 92 (1 pt 1), 73-81.

Sedation in allergic rhinitis is caused by the condition and not by the antihistamine
treatment.
Allergy, 51, 893-906.

Cetirizine: A reappraisal of its pharmacological properties and therapeutic use in selected
allergic disorders.
Drugs, 46 (6), 1055-1080.

Stanley, N. (1997)
Actigraphy in psychopharmacology.
In: Human Psychopharmacology, Methods & Measures, Volume 6, , Edited by
Hindmarch I. & Stonier P.D. John Wiley & Sons, Chichester, UK.

Comparison of the effects of astemizole/pseudoephedrine and
triprodilide/pseudoephedrine on CNS activity, cognitive function and psychomotor
function: a placebo controlled, crossover trial.
International Clinical Psychopharmacology, 11, 31-36.

Starmer, G. (1985)
Antihistamines and highway safety.
Accident Analysis and Prevention, 17, 311-317.
Update on collecting ADRs and new methods of signal generation.
Reactions, 718, 3-5.

Sternberg, S. (1966)
High speed scanning in human memory.

Memory scanning: mental processes revealed by reaction time experiments.
American Scientist, 57, 421-457.

Studies into the possible central effects of the H₁ receptor antagonist, fexofenadine.
International Archives of allergy and immunology, 118 (2-4), 338.

SCH434: a new antihistamine/decongestant for seasonal allergic rhinitis.
Journal of Allergy and Clinical Immunology, 83, 2083-1090.

Effects of zopiclone and benzodiazepine hypnotics on search in short-term memory.
Neuropsychobiology, 12, 244-248.

Subhan, Z. and Hindmarch, I. (1984b)
The psychopharmacological effects of ginkgo biloba extract in normal healthy volunteers.
International Journal of Clinical Psychopharmacology, 4, 2, 89-93.

Subhan, Z. and Hindmarch, I. (1985)
Psychopharmacological effects of vinpocetine in normal healthy volunteers.
European Journal of Clinical Pharmacology, 28, 567-571.

Alprazolam and lorazepam: Single and multiple dose effects on psychomotor skills and sleep.

Comparison of the efficacy of astemizole, diphenhydramine, and hydroxyzine in the treatment of chronic idiopathic urticaria.
Clinical and Investigative Medicine, 11, C5.

The efficacy and safety of fexofenadine HCl and pseudoephedrine, alone and in combination, in seasonal allergic rhinitis.
Journal of Allergy and Clinical Immunology, 104 (1), 100-106.
Effects of a sedative and of a non-sedative H₁ antihistamine on the event related potential in normal volunteers.
Psychopharmacology, 98, 425-429.

Astemizole in perennial allergic rhinitis with seasonal exacerbation: a placebo controlled double blind study.
Annals of Allergy, 63, 493-494.

Tamasky, P.R. and van Arsdale, P.P. (1990)
Antihistamine therapy in allergic rhinitis.
The Journal of Family Practice, 30(1), 71-80.

Antihistamine effects on the central nervous system, cognitive performance and subjective states.
Neuropsychobiology, 29 (2), 97-104.

Double blind controlled study of clemastine fumarate, chlorpheniramine and placebo in patients with seasonal allergic rhinitis.
Annals of Allergy, 38, 169-174.

Why are non-sedating antihistamines non-sedating?
Clinical and Experimental Allergy, 29 (3), 13-18.

Efficacy and safety of fexofenadine HCl in fall seasonal allergic rhinitis. (abstract)
Journal of Allergy and Clinical Immunology, 97 (1/3); 435.

Todd, G. (1975)
Double blind trials of clemastine in allergic rhinitis.
Current Medical Research and Opinion, 3, 126-1131.


Turner, P. (1968)
Critical Flicker Frequency and centrally acting drugs.

Effectiveness of clemastine fumarate for the treatment of rhinorrhoea and sneezing associated with the common cold.
Clinical Infectious Diseases, 25 (4), 824-830.


Effects of mizolastine and clemastine on actual car driving and psychomotor
performance in healthy volunteers.
European Journal of Clinical Pharmacology, 47, 253-259.

Vuurman, E.F.P.M., van Veggel, L.M.A., Uiterwijk, M.C., Leutner, D. and O’Hanlon,
Seasonal allergic rhinitis and antihistamine effects on children’s learning.
Annals of Allergy, 71 (2), 121-126.

Vuurman, E.F.P.M., van Veggel, L.M.A., Sanders, R.L., Muntjewerff, N.D. and
Effects of Semprex -D and diphenhydramine on learning in young adults with seasonal
allergic rhinitis.
Annals of Allergy, Asthma and Immunology, 76 (3), 247-252.

Wahlgren, C.F., Hagermark, O. and Bergstrom, R. (1990)
The antipruritic effect of a sedative and a non-sedative antihistamine in atopic dermatitis.
British Journal of Dermatology, 122, 545-551.

Simulated assembly line performance following ingestion of cetirizine and hydroxyzine.
Annals of Allergy, 69, 195-200.

Drugs detected in fatally injured drivers in the province of Ontario.
In: Goldberg L (Eds.). Alcohol, Drugs and Traffic Safety, Volume 1, Stockholm:
Almquist and Wiksell, 203-217.

Watanabe, K.L. (1931)
Quantitative Untersuchungenuber den Gehalt an Darkmontrahiereden Stoffen von Lunge
und Leber bei Meersschweinchen in Stadium der Eiweissensensibilisierung und in
anaplyaktischer Shock.
Zeitschrift fur Immunitatserforschung Experimentelle und Therapie, 72, 50-52.

West, S., Brandon, B. and Stolley, P. (1975)
A review of antihistamines and the common cold.
Pediatrics, 56, 100-107.

Behavioural effects of histamine and its antagonists: a review.
Psychopharmacology, 95, 1-14.

Absence of an effect of terfenadine on guinea pig brain histamine H1 receptor in vivo
determined by receptor binding techniques.
Arzneimittel Forschung, 32 (II, 9a), 1167-1170.


Wong, L. and Hendeles, L. (1981)
Pharmacological prophylaxis of allergic rhinitis: relative efficacy of hydroxyzine and chlorpheniramine.
Journal of Allergy and Clinical Immunology, 67, 223-228.

Astemizole and terfenadine compared in hay fever.
The Practitioner, 230, 41-44.

Choosing an antihistamine.

Wood, S.F., Kennedy, R.S. and Graybiel, A. (1965)
Aerospace Medicine, 36, 1-4.

Woodbaker, R., Emanuel, M.B., Hutchinson, K. and Holgate, P.H. (1993)
The time course of action of three differing doses of norebastine, a novel H1 receptor antagonist, on histamine-induced skin wheals and the relationship to plasma drug concentrations in normal human volunteers.

Pharmacology and toxicology of non-classical antihistamines.
Cutis,, 42, 5-10.

Woodward, J.K. (1990)
Pharmacology of antihistamines.
Journal of Allergy & Clinical Immunology, 86 (4, pt II), 606-612.

Cardiac actions of antihistamines.
Annual Review of Pharmacology and Toxicology, 36, 233-252.

Experimental psychology.
Methuen, London.

Wirksamkeit und verträglichkeit von neuartigen antiallergica bei akuter pollenrhinitis.
Schweizerische Rundschau für Medizin Praxis, 71 (36), 1367-1372.

Comparison of terfenadine in two dose regimens in the treatment of seasonal allergic rhinitis. (abstract)
Presented at the American Academy of Allergy and Immunology 44th Annual Meeting, Anaheim, California.
Zaun, H. and Peter, U. (1990)
Wirksamkeit und verträglichkeit von loratadin im vergleich zu ketotifen bei saisonaler allergischer rhinitis.
Allergologie, 13, 29-32.

Astemizole en terfenadine: comparaison de l’effet therapeutique dans le rhinite polinique.
Revue Medicale de la Suisse Romande, 107, 857-861.

Double blind, crossover study of high dose cetirizine in cholinergic urticaria.
Dermatology, 193 (4), 324-327.
Appendix 1  
Table of Means

Experiment One

Table One: Day One – Mean Weal Area (mm²) and standard deviations (s.d.):

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Fexofenadine 40mg b.d.</th>
<th>Loratadine 10mg o.d</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
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<td>29.77 (10.03)</td>
<td>31.43 (11.95)</td>
<td>31.08 (8.89)</td>
</tr>
<tr>
<td>0.0</td>
<td>28.30 (7.57)</td>
<td>28.90 (7.82)</td>
<td>28.47 (5.73)</td>
</tr>
<tr>
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<td>30.57 (8.44)</td>
<td>31.11 (12.76)</td>
</tr>
<tr>
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<td>27.72 (5.97)</td>
<td>30.23 (6.29)</td>
</tr>
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<td>26.93 (9.71)</td>
<td>31.50 (9.67)</td>
</tr>
<tr>
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<td>28.38 (7.38)</td>
<td>24.85 (7.08)</td>
<td>31.80 (10.47)</td>
</tr>
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<td>26.69 (9.03)</td>
<td>23.56 (10.19)</td>
<td>29.62 (11.93)</td>
</tr>
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<td>21.00 (7.45)</td>
<td>28.86 (10.63)</td>
</tr>
<tr>
<td>4.0</td>
<td>20.29 (8.23)</td>
<td>19.93 (7.13)</td>
<td>30.57 (13.66)</td>
</tr>
<tr>
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<td>22.96 (11.34)</td>
<td>22.59 (8.70)</td>
<td>27.78 (11.29)</td>
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<td>18.72 (6.00)</td>
<td>28.10 (10.25)</td>
</tr>
<tr>
<td>8.0</td>
<td>22.03 (8.94)</td>
<td>21.60 (7.77)</td>
<td>30.23 (13.39)</td>
</tr>
<tr>
<td>12.0</td>
<td>22.46 (9.06)</td>
<td>19.42 (6.34)</td>
<td>27.99 (8.92)</td>
</tr>
<tr>
<td>18.0</td>
<td>17.12 (8.51)</td>
<td>17.11 (5.41)</td>
<td>28.32 (16.55)</td>
</tr>
<tr>
<td>24.0</td>
<td>19.46 (7.31)</td>
<td>20.60 (7.88)</td>
<td>28.21 (15.30)</td>
</tr>
</tbody>
</table>
Table Two: Day Four – Mean Weal Area (mm$^2$) and standard deviations (s.d.):

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Fexofenadine 40 mg b.d.</th>
<th>Loratadine 10mg o.d</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
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<td>23.83 (9.21)</td>
<td>19.27 (6.98)</td>
<td>25.89 (9.77)</td>
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<td>19.41 (6.52)</td>
<td>28.62 (9.75)</td>
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<td>21.66 (5.66)</td>
<td>23.10 (6.96)</td>
<td>28.03 (12.10)</td>
</tr>
<tr>
<td>0.75</td>
<td>23.63 (6.93)</td>
<td>22.59 (8.92)</td>
<td>27.08 (8.17)</td>
</tr>
<tr>
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<td>19.15 (7.59)</td>
<td>23.77 (6.02)</td>
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<tr>
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<td>24.74 (6.92)</td>
</tr>
<tr>
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<td>19.39 (9.34)</td>
<td>21.38 (7.90)</td>
</tr>
<tr>
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<td>15.66 (6.70)</td>
<td>18.04 (8.14)</td>
<td>24.54 (7.08)</td>
</tr>
<tr>
<td>4.0</td>
<td>18.08 (7.51)</td>
<td>16.96 (6.65)</td>
<td>26.14 (9.79)</td>
</tr>
<tr>
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<td>24.91 (6.32)</td>
</tr>
<tr>
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<td>15.58 (5.40)</td>
<td>24.26 (7.01)</td>
</tr>
<tr>
<td>8.0</td>
<td>18.82 (5.02)</td>
<td>19.21 (10.68)</td>
<td>24.63 (7.05)</td>
</tr>
<tr>
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<td>18.22 (5.02)</td>
<td>16.65 (6.96)</td>
<td>27.09 (8.84)</td>
</tr>
<tr>
<td>18.0</td>
<td>13.54 (5.25)</td>
<td>13.39 (6.91)</td>
<td>23.07 (9.85)</td>
</tr>
<tr>
<td>24.0</td>
<td>16.55 (4.49)</td>
<td>14.22 (4.49)</td>
<td>24.91 (9.37)</td>
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</tbody>
</table>
Table Three: Day One – Mean Flare Area (mm\(^2\)) and standard deviations (s.d.):

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Fexofenadine 40 mg b.d.</th>
<th>Loratadine 10mg o.d.</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
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<td>491.02 (353.55)</td>
<td>562.03 (368.56)</td>
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<td>526.41 (414.75)</td>
<td>501.14 (349.98)</td>
<td>567.67 (231.37)</td>
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<tr>
<td>0.5</td>
<td>547.56 (293.63)</td>
<td>537.01 (349.74)</td>
<td>552.27 (313.50)</td>
</tr>
<tr>
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<td>426.53 (331.64)</td>
<td>490.25 (377.43)</td>
<td>463.12 (398.34)</td>
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<td>418.77 (317.94)</td>
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<td>338.70 (280.40)</td>
<td>412.27 (267.20)</td>
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<td>507.16 (280.04)</td>
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<td>227.50 (234.99)</td>
<td>566.46 (273.27)</td>
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<td>101.61 (165.41)</td>
<td>383.51 (272.69)</td>
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<td>104.22 (158.32)</td>
<td>205.56 (239.01)</td>
<td>462.59 (393.96)</td>
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<td>501.32 (235.27)</td>
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<td>329.46 (382.68)</td>
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<td>224.75 (265.94)</td>
<td>621.26 (566.02)</td>
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<tr>
<td>24.0</td>
<td>166.42 (162.82)</td>
<td>260.98 (356.15)</td>
<td>583.69 (366.76)</td>
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</table>
Table Four: Day Four – Mean Flare Area (mm\(^2\)) and standard deviations (s.d.):

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Fexofenadine 40 mg b.d.</th>
<th>Loratadine 10mg o.d</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.5</td>
<td>143.49 (178.01)</td>
<td>111.61 (197.13)</td>
<td>467.03 (214.66)</td>
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<tr>
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<td>86.67 (134.18)</td>
<td>527.71 (363.21)</td>
</tr>
<tr>
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<td>126.66 (172.34)</td>
<td>501.02 (291.60)</td>
</tr>
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<td>409.82 (231.16)</td>
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<td>343.73 (304.04)</td>
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<td>75.21 (164.47)</td>
<td>396.07 (240.94)</td>
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<td>302.48 (181.72)</td>
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<td>362.15 (251.54)</td>
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<td>464.09 (291.12)</td>
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<td>113.74 (221.59)</td>
<td>716.24 (459.05)</td>
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<td>142.66 (303.77)</td>
<td>579.44 (420.66)</td>
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<td>78.41 (101.25)</td>
<td>110.58 (265.61)</td>
<td>638.86 (463.30)</td>
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</table>
### Table 5: Mean Weal Area (mm²) and standard deviations (s.d.):

(Fexo = fexofenadine, Lor = loratadine, Prom = promethazine)

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Fexo 80mg</th>
<th>Fexo 120mg</th>
<th>Fexo 180mg</th>
<th>Lor 10mg</th>
<th>Prom 30mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
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<td>-0.5</td>
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<td>35.68(10.06)</td>
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<td>32.28(7.29)</td>
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<td>35.88(11.83)</td>
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<td>36.97(6.91)</td>
<td>32.09(10.52)</td>
<td>34.03(8.79)</td>
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<td>32.44(10.69)</td>
<td>33.32(8.53)</td>
<td>34.74(10.17)</td>
<td>32.54(6.80)</td>
<td>37.08(11.58)</td>
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<td>32.69(12.57)</td>
<td>28.31(10.09)</td>
<td>33.13(99.89)</td>
<td>28.42(9.27)</td>
<td>36.57(9.94)</td>
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<td>26.23(8.94)</td>
<td>24.63(12.06)</td>
<td>33.61(7.58)</td>
<td>25.08(10.73)</td>
<td>30.22(7.81)</td>
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<td>17.21(10.53)</td>
<td>29.48(10.55)</td>
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<td>19.08(10.01)</td>
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<td>20.49(9.93)</td>
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<td>12.63(5.13)</td>
<td>10.65(7.55)</td>
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<td>22.67(10.10)</td>
<td>26.43(14.37)</td>
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</table>
Table 6: Mean Flare Area (mm$^2$) and standard deviations (s.d.):

(Fexo = fexofenadine, Lor = loratadine, Prom = promethazine)

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Fexo 80mg</th>
<th>Fexo 120mg</th>
<th>Fexo 180mg</th>
<th>Lor 10mg</th>
<th>Prom 30mg</th>
<th>Placebo</th>
</tr>
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<td>728.45</td>
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<td>710.51</td>
<td>680.83</td>
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<tr>
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<td>(334.50)</td>
<td>(283.19)</td>
<td>(381.84)</td>
<td>(436.33)</td>
<td>(514.65)</td>
</tr>
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<td>757.24</td>
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<td>785.48</td>
<td>789.69</td>
<td>728.05</td>
<td>777.43</td>
</tr>
<tr>
<td></td>
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<td>(322.10)</td>
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Experiment Three

Table 7: Critical Flicker Fusion: Mean values (Hz) and standard errors (S.E.M.) for all treatment conditions:
(Fexo = fexofenadine, Lor = loratadine, Prom = promethazine)

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Fexo 80mg</th>
<th>Fexo 120mg</th>
<th>Fexo 180mg</th>
<th>Lor 10mg</th>
<th>Prom 30mg</th>
<th>Placebo</th>
</tr>
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<tbody>
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<td>30.80</td>
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<td>(0.69)</td>
<td>(0.61)</td>
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<td>(0.72)</td>
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<td>(0.61)</td>
<td>(0.64)</td>
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Table 8: Total Reaction Time: Mean values (msec) and standard errors (S.E.M.) for all treatment conditions:
(Fexo = fexofenadine, Lor = loratadine, Prom = promethazine)

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Fexo 80mg</th>
<th>Fexo 120mg</th>
<th>Fexo 180mg</th>
<th>Lor 10mg</th>
<th>Prom 30mg</th>
<th>Placebo</th>
</tr>
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<td>(13.79)</td>
<td>(14.45)</td>
<td>(12.69)</td>
<td>(16.71)</td>
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<td>584.47</td>
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<td>(15.64)</td>
<td>(17.29)</td>
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<td>(15.79)</td>
<td>(19.40)</td>
<td>(17.61)</td>
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<td>615.88</td>
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<td>(15.74)</td>
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<td>590.80</td>
<td>578.78</td>
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<td>(14.81)</td>
<td>(17.58)</td>
<td>(17.42)</td>
<td>(15.14)</td>
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<td>(14.37)</td>
<td>(14.72)</td>
<td>(14.89)</td>
<td>(15.06)</td>
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Table 9:  Recognition Reaction Time: Mean values (msec) and standard errors (S.E.M.) for all treatment conditions:
(Fexo = fexofenadine, Lor = loratadine, Prom = promethazine)

<table>
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<tr>
<th>Time (hrs)</th>
<th>Fexo 80mg</th>
<th>Fexo 120mg</th>
<th>Fexo 180mg</th>
<th>Lor 10mg</th>
<th>Prom 30mg</th>
<th>Placebo</th>
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<td>375.60 (8.90)</td>
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<td>382.80 (11.10)</td>
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</table>

Table 10:  Line Analogue Rating Scales for Sedation: Mean values (msec) and standard errors (S.E.M.) for all treatment conditions:
(Fexo = fexofenadine, Lor = loratadine, Prom = promethazine)

<table>
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<th>Time (hrs)</th>
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<th>Fexo 120mg</th>
<th>Fexo 180mg</th>
<th>Lor 10mg</th>
<th>Prom 30mg</th>
<th>Placebo</th>
</tr>
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<td>50.71 (1.60)</td>
</tr>
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<td>52.82 (1.31)</td>
<td>52.40 (1.59)</td>
<td>57.34 (1.71)</td>
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<td>47.96 (1.47)</td>
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### Table 11: Critical Flicker Fusion: Individual data, together with mean values (Hz) and standard deviations (s.d.) for all treatment conditions:

<table>
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<th>Minimum</th>
<th>Maximum</th>
<th>s.d.</th>
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<td>2.557540</td>
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<td>34.50000</td>
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<td>2.290750</td>
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<td>37.83333</td>
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<tr>
<td>G1</td>
<td>30.80556</td>
<td>25.66667</td>
<td>35.33333</td>
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<td>2.449490</td>
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<tr>
<td>H6</td>
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<td>2.455007</td>
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</table>

A = cetirizine 10mg, B = loratadine 10mg, C = promethazine, D = placebo,
E = cetirizine 2.5mg, F = cetirizine 5mg, G = loratadine 40mg, H = loratadine 20mg
Table 12: Total Reaction Time: Individual data, together with mean values (msec) and standard error (s.e.) for all treatment conditions:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
<th>s.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0</td>
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<td>537.1200</td>
<td>915.990</td>
<td>19.75810</td>
</tr>
<tr>
<td>A1</td>
<td>686.3664</td>
<td>520.4100</td>
<td>1008.160</td>
<td>25.77675</td>
</tr>
<tr>
<td>A3</td>
<td>666.9529</td>
<td>500.0100</td>
<td>885.360</td>
<td>18.38329</td>
</tr>
<tr>
<td>A6</td>
<td>665.2227</td>
<td>527.1700</td>
<td>1058.520</td>
<td>24.27497</td>
</tr>
<tr>
<td>B0</td>
<td>689.9724</td>
<td>501.1000</td>
<td>947.860</td>
<td>24.22007</td>
</tr>
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<td>895.470</td>
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</tr>
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<td>B3</td>
<td>662.7408</td>
<td>522.1100</td>
<td>841.250</td>
<td>15.60357</td>
</tr>
<tr>
<td>B6</td>
<td>682.9104</td>
<td>513.4500</td>
<td>1067.360</td>
<td>27.21389</td>
</tr>
<tr>
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<td>642.9713</td>
<td>528.3900</td>
<td>739.290</td>
<td>15.68890</td>
</tr>
<tr>
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<td>822.100</td>
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</tr>
<tr>
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</tr>
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<td>1008.200</td>
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</tr>
<tr>
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<td>504.8100</td>
<td>1110.460</td>
<td>29.33147</td>
</tr>
<tr>
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<td>673.5912</td>
<td>433.4800</td>
<td>805.160</td>
<td>17.38363</td>
</tr>
<tr>
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<td>664.3996</td>
<td>564.3700</td>
<td>808.580</td>
<td>13.51443</td>
</tr>
<tr>
<td>D6</td>
<td>661.8896</td>
<td>446.1900</td>
<td>869.220</td>
<td>17.69174</td>
</tr>
<tr>
<td>E0</td>
<td>674.5150</td>
<td>550.1700</td>
<td>865.300</td>
<td>21.96636</td>
</tr>
<tr>
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<td>568.1700</td>
<td>986.440</td>
<td>18.29951</td>
</tr>
<tr>
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<td>532.2500</td>
<td>882.930</td>
<td>17.49408</td>
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<tr>
<td>E6</td>
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</tr>
<tr>
<td>F0</td>
<td>651.7572</td>
<td>493.2000</td>
<td>816.730</td>
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<tr>
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<td>459.0300</td>
<td>797.750</td>
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<td>525.5100</td>
<td>940.010</td>
<td>22.83415</td>
</tr>
<tr>
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<td>507.5300</td>
<td>1466.840</td>
<td>40.11808</td>
</tr>
<tr>
<td>G3</td>
<td>744.9796</td>
<td>547.1300</td>
<td>1431.050</td>
<td>40.45568</td>
</tr>
<tr>
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<td>539.9500</td>
<td>824.110</td>
<td>16.49654</td>
</tr>
<tr>
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<td>552.9900</td>
<td>1236.610</td>
<td>35.22485</td>
</tr>
<tr>
<td>H1</td>
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</tr>
<tr>
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<td>678.8718</td>
<td>527.8300</td>
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<tr>
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<td>714.0019</td>
<td>524.1500</td>
<td>1573.040</td>
<td>46.70329</td>
</tr>
</tbody>
</table>

A = cetirizine 10mg, B = loratadine 10mg, C = promethazine, D = placebo, E = cetirizine 2.5mg, F = cetirizine 5mg, G = loratadine 40mg, H = loratadine 20mg
Table 13: Line Analogue Rating Scales for sedation: Individual data, together with mean values (mm) and standard deviations (s.d.) for all treatment conditions:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
<th>s.d.</th>
</tr>
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<td>6.33053</td>
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<td>33.5000</td>
<td>78.0000</td>
<td>8.84652</td>
</tr>
<tr>
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<td>38.0000</td>
<td>82.5000</td>
<td>9.50391</td>
</tr>
<tr>
<td>A6</td>
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<td>37.5000</td>
<td>71.0000</td>
<td>7.81787</td>
</tr>
<tr>
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<td>75.0000</td>
<td>5.47458</td>
</tr>
<tr>
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<td>99.0000</td>
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<tr>
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<td>37.0000</td>
<td>80.5000</td>
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</tr>
<tr>
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<td>33.5000</td>
<td>67.5000</td>
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</tr>
<tr>
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<td>67.5000</td>
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</tr>
<tr>
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<td>14.0000</td>
<td>78.0000</td>
<td>11.02098</td>
</tr>
<tr>
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<td>53.16667</td>
<td>14.5000</td>
<td>100.000</td>
<td>14.79253</td>
</tr>
</tbody>
</table>

A = cetirizine 10mg, B = loratadine 10mg, C = promethazine, D = placebo,
E = cetirizine 2.5mg, F = cetirizine 5mg, G = loratadine 40mg, H = loratadine 20mg
**Experiment Five**

**Table 14:** Critical Flicker Fusion: Individual data, together with mean values (Hz) and standard deviations (s.d.) for all treatment conditions:

(Eba = ebastine, Trip = triprolidine, Terf = terfenadine)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eba 10mg</th>
<th>Eba 20mg</th>
<th>Eba 40mg</th>
<th>Trip 5mg</th>
<th>Terf 60mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>28.2 (2.5)</td>
<td>28.2 (3.2)</td>
<td>28.5 (2.5)</td>
<td>27.7 (2.6)</td>
<td>28.2 (2.5)</td>
<td>28.3 (3.0)</td>
</tr>
<tr>
<td>0.5</td>
<td>27.90 (2.3)</td>
<td>27.9 (2.8)</td>
<td>28.2 (2.3)</td>
<td>28.0 (2.3)</td>
<td>27.7 (2.3)</td>
<td>28.2 (3.4)</td>
</tr>
<tr>
<td>1.5</td>
<td>27.6 (2.5)</td>
<td>27.8 (2.8)</td>
<td>27.8 (2.2)</td>
<td>27.7 (2.4)</td>
<td>26.3 (1.9)</td>
<td>28.2 (3.4)</td>
</tr>
<tr>
<td>3.5</td>
<td>28.0 (2.2)</td>
<td>27.7 (2.8)</td>
<td>27.9 (1.7)</td>
<td>27.5 (2.2)</td>
<td>27.4 (2.1)</td>
<td>28.2 (3.4)</td>
</tr>
<tr>
<td>6.5</td>
<td>28.1 (2.2)</td>
<td>27.9 (2.4)</td>
<td>27.9 (2.0)</td>
<td>27.7 (2.7)</td>
<td>28.0 (2.3)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 15:** Recognition Reaction Time: Individual data, together with mean values (msec) and standard deviations (s.d.) for all treatment conditions:

(Eba = ebastine, Trip = triprolidine, Terf = terfenadine)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eba 10mg</th>
<th>Eba 20mg</th>
<th>Eba 40mg</th>
<th>Trip 5mg</th>
<th>Terf 60mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>380.7 (54.1)</td>
<td>385.8 (61.4)</td>
<td>363.9 (42.3)</td>
<td>365.3 (39.5)</td>
<td>371.7 (46.2)</td>
<td>376.3 (56.2)</td>
</tr>
<tr>
<td>0.5</td>
<td>372.1 (43.8)</td>
<td>379.8 (50.0)</td>
<td>380.1 (49.9)</td>
<td>381.4 (43.1)</td>
<td>373.6 (53.3)</td>
<td>375.9 (54.6)</td>
</tr>
<tr>
<td>1.5</td>
<td>372.6 (46.9)</td>
<td>398.7 (43.7)</td>
<td>377.8 (45.3)</td>
<td>386.7 (46.1)</td>
<td>383.8 (62.6)</td>
<td>375.0 (54.7)</td>
</tr>
<tr>
<td>3.5</td>
<td>385.9 (49.4)</td>
<td>392.4 (60.6)</td>
<td>378.4 (46.2)</td>
<td>394.4 (78.5)</td>
<td>385.8 (51.4)</td>
<td>377.0 (64.1)</td>
</tr>
<tr>
<td>6.5</td>
<td>386.4 (59.3)</td>
<td>389.8 (49.7)</td>
<td>392.8 (50.7)</td>
<td>391.8 (42.7)</td>
<td>378.5 (49.6)</td>
<td>375.3 (54.0)</td>
</tr>
</tbody>
</table>
Table 16: Total Reaction Time: Individual data, together with mean values (msec) and standard deviations (s.d.) for all treatment conditions:
(Eba = ebastine, Trip = triprolidine, Terf = terfenadine)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eba 10mg</th>
<th>Eba 20mg</th>
<th>Eba 40mg</th>
<th>Trip 5mg</th>
<th>Ter 60mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>555.2 (65.1)</td>
<td>555.1 (70.1)</td>
<td>563.2 (57.4)</td>
<td>546.4 (66.5)</td>
<td>538.5 (57.7)</td>
<td>554.0 (75.3)</td>
</tr>
<tr>
<td>0.5</td>
<td>545.2 (56.4)</td>
<td>556.6 (59.5)</td>
<td>556.1 (64.9)</td>
<td>558.0 (60.0)</td>
<td>544.2 (68.1)</td>
<td>539.3 (66.6)</td>
</tr>
<tr>
<td>1.5</td>
<td>553.6 (64.4)</td>
<td>567.8 (52.8)</td>
<td>556.0 (75.2)</td>
<td>565.2 (80.1)</td>
<td>563.3 (78.5)</td>
<td>547.1 (69.3)</td>
</tr>
<tr>
<td>3.5</td>
<td>561.9 (72.0)</td>
<td>566.1 (68.8)</td>
<td>554.2 (68.2)</td>
<td>571.3 (111.5)</td>
<td>563.0 (59.9)</td>
<td>549.8 (79.0)</td>
</tr>
<tr>
<td>6.5</td>
<td>555.4 (71.6)</td>
<td>563.8 (64.4)</td>
<td>575.3 (86.6)</td>
<td>569.7 (75.4)</td>
<td>562.9 (63.4)</td>
<td>554.2 (78.3)</td>
</tr>
</tbody>
</table>

Table 17: Compensatory Tracking Task – Reaction time: Individual data, together with mean values (msec) and standard deviations (s.d.) for all treatment conditions:
(Eba = ebastine, Trip = triprolidine, Terf = terfenadine)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eba 10mg</th>
<th>Eba 20mg</th>
<th>Eba 40mg</th>
<th>Trip 5mg</th>
<th>Ter 60mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>408.3 (79.8)</td>
<td>405.4 (68.8)</td>
<td>398.3 (54.6)</td>
<td>418.9 (79.3)</td>
<td>412.0 (68.3)</td>
<td>403.8 (69.4)</td>
</tr>
<tr>
<td>1.5</td>
<td>410.3 (74.8)</td>
<td>419.5 (72.3)</td>
<td>408.5 (67.9)</td>
<td>435.0 (87.0)</td>
<td>434.2 (71.9)</td>
<td>418.6 (68.8)</td>
</tr>
<tr>
<td>3.5</td>
<td>414.2 (85.6)</td>
<td>425.2 (73.9)</td>
<td>416.9 (65.8)</td>
<td>430.1 (74.4)</td>
<td>421.8 (68.0)</td>
<td>410.2 (64.3)</td>
</tr>
<tr>
<td>6.5</td>
<td>406.7 (67.3)</td>
<td>420.5 (71.7)</td>
<td>422.5 (80.6)</td>
<td>439.6 (89.3)</td>
<td>428.8 (78.0)</td>
<td>409.8 (56.5)</td>
</tr>
</tbody>
</table>
Table 18: Compensatory Tracking Task – Tracking Accuracy: Individual data, together with mean values (RMS) and standard deviations (s.d.) for all treatment conditions:

(\text{Eba} = \text{ebastine}, \text{Trip} = \text{triprolidine}, \text{Terf} = \text{terfenadine})

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eba 10mg</th>
<th>Eba 20mg</th>
<th>Eba 40mg</th>
<th>Trip 5mg</th>
<th>Ter 60mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>8.3</td>
<td>8.3</td>
<td>8.0</td>
<td>8.2</td>
<td>8.4</td>
<td>7.8</td>
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<tr>
<td></td>
<td>(2.2)</td>
<td>(2.5)</td>
<td>(1.7)</td>
<td>(1.6)</td>
<td>(1.7)</td>
<td>(1.2)</td>
</tr>
<tr>
<td><strong>1.5</strong></td>
<td>8.1</td>
<td>8.0</td>
<td>7.6</td>
<td>9.6</td>
<td>9.0</td>
<td>7.7</td>
</tr>
<tr>
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<td>(2.2)</td>
<td>(2.0)</td>
<td>(1.9)</td>
<td>(5.5)</td>
<td>(2.4)</td>
<td>(1.5)</td>
</tr>
<tr>
<td><strong>3.5</strong></td>
<td>7.9</td>
<td>8.6</td>
<td>7.6</td>
<td>9.3</td>
<td>8.5</td>
<td>7.8</td>
</tr>
<tr>
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<td>(2.1)</td>
<td>(2.8)</td>
<td>(2.1)</td>
<td>(4.7)</td>
<td>(2.6)</td>
<td>(1.7)</td>
</tr>
<tr>
<td><strong>6.5</strong></td>
<td>8.1</td>
<td>8.6</td>
<td>8.5</td>
<td>9.5</td>
<td>8.2</td>
<td>7.7</td>
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<tr>
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<td>(2.1)</td>
<td>(3.1)</td>
<td>(3.5)</td>
<td>(4.9)</td>
<td>(2.0)</td>
<td>(1.5)</td>
</tr>
</tbody>
</table>

Table 19: Line Analogue Rating Scales for Sedation: Individual data, together with mean values (mm) and standard deviations (s.d.) for all treatment conditions:

(\text{Eba} = \text{ebastine}, \text{Trip} = \text{triprolidine}, \text{Terf} = \text{terfenadine})

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eba 10mg</th>
<th>Eba 20mg</th>
<th>Eba 40mg</th>
<th>Trip 5mg</th>
<th>Ter 60mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>52.1</td>
<td>52.0</td>
<td>54.0</td>
<td>55.6</td>
<td>53.9</td>
<td>55.0</td>
</tr>
<tr>
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<td>(2.5)</td>
<td>(6.7)</td>
<td>(5.6)</td>
<td>(7.6)</td>
<td>(5.8)</td>
<td>(6.0)</td>
</tr>
<tr>
<td><strong>0.5</strong></td>
<td>53.6</td>
<td>55.0</td>
<td>52.8</td>
<td>55.1</td>
<td>52.1</td>
<td>53.3</td>
</tr>
<tr>
<td></td>
<td>(6.6)</td>
<td>(4.8)</td>
<td>(6.6)</td>
<td>(6.8)</td>
<td>(3.8)</td>
<td>(6.0)</td>
</tr>
<tr>
<td><strong>1.5</strong></td>
<td>56.7</td>
<td>55.4</td>
<td>54.2</td>
<td>58.0</td>
<td>61.8</td>
<td>56.6</td>
</tr>
<tr>
<td></td>
<td>(9.3)</td>
<td>(5.8)</td>
<td>(5.9)</td>
<td>(7.3)</td>
<td>(8.2)</td>
<td>(5.9)</td>
</tr>
<tr>
<td><strong>3.5</strong></td>
<td>56.3</td>
<td>55.7</td>
<td>55.3</td>
<td>57.8</td>
<td>56.3</td>
<td>55.7</td>
</tr>
<tr>
<td></td>
<td>(5.4)</td>
<td>(5.5)</td>
<td>(5.9)</td>
<td>(9.1)</td>
<td>(7.6)</td>
<td>(6.9)</td>
</tr>
<tr>
<td><strong>6.5</strong></td>
<td>56.7</td>
<td>56.5</td>
<td>58.1</td>
<td>60.5</td>
<td>55.3</td>
<td>56.5</td>
</tr>
<tr>
<td></td>
<td>(4.6)</td>
<td>(9.2)</td>
<td>(8.9)</td>
<td>(11.4)</td>
<td>(7.1)</td>
<td>(7.7)</td>
</tr>
</tbody>
</table>
Experiment 6

Table 20: Mean pre-treatment scores (standard deviations) for CFF together with mean changes (standard deviations) from baseline for days 1 and 5 for all treatment conditions:
(Eba = ebastine, Trip = triprolidine)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eba 10mg</th>
<th>Eba 20mg</th>
<th>Eba 30mg</th>
<th>Trip 10mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 H0</td>
<td>28.110</td>
<td>27.615</td>
<td>28.110</td>
<td>27.983</td>
<td>27.710</td>
</tr>
<tr>
<td></td>
<td>(3.796)</td>
<td>(3.683)</td>
<td>(3.796)</td>
<td>(3.615)</td>
<td>(3.605)</td>
</tr>
<tr>
<td>D1 H1</td>
<td>-1.055</td>
<td>0.196</td>
<td>-0.173</td>
<td>0.159</td>
<td>0.053</td>
</tr>
<tr>
<td></td>
<td>(1.349)</td>
<td>(1.221)</td>
<td>(1.297)</td>
<td>(1.458)</td>
<td>(1.066)</td>
</tr>
<tr>
<td>D1 H2</td>
<td>-1.652</td>
<td>-0.515</td>
<td>-0.862</td>
<td>-0.724</td>
<td>-1.830</td>
</tr>
<tr>
<td></td>
<td>(1.413)</td>
<td>(0.921)</td>
<td>(1.317)</td>
<td>(0.792)</td>
<td>(1.161)</td>
</tr>
<tr>
<td>D1 H4</td>
<td>-1.187</td>
<td>-1.026</td>
<td>-1.137</td>
<td>-0.856</td>
<td>-1.062</td>
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<tr>
<td></td>
<td>(1.160)</td>
<td>(0.829)</td>
<td>(1.557)</td>
<td>(1.137)</td>
<td>(1.692)</td>
</tr>
<tr>
<td>D1 H8</td>
<td>-1.978</td>
<td>-1.770</td>
<td>-1.465</td>
<td>-1.676</td>
<td>-1.519</td>
</tr>
<tr>
<td></td>
<td>(0.901)</td>
<td>(0.766)</td>
<td>(1.778)</td>
<td>(1.189)</td>
<td>(1.297)</td>
</tr>
<tr>
<td>D5 H0</td>
<td>-0.773</td>
<td>-0.357</td>
<td>-0.307</td>
<td>0.430</td>
<td>0.392</td>
</tr>
<tr>
<td></td>
<td>(0.971)</td>
<td>(0.867)</td>
<td>(1.163)</td>
<td>(1.023)</td>
<td>(0.903)</td>
</tr>
<tr>
<td>D5 H1</td>
<td>-1.168</td>
<td>-0.374</td>
<td>0.092</td>
<td>0.357</td>
<td>-0.163</td>
</tr>
<tr>
<td></td>
<td>(1.568)</td>
<td>(1.874)</td>
<td>(0.986)</td>
<td>(1.447)</td>
<td>(1.126)</td>
</tr>
<tr>
<td>D5 H2</td>
<td>-1.373</td>
<td>-0.835</td>
<td>-1.318</td>
<td>-0.405</td>
<td>-1.038</td>
</tr>
<tr>
<td></td>
<td>(1.103)</td>
<td>(1.526)</td>
<td>(1.177)</td>
<td>(1.566)</td>
<td>(0.914)</td>
</tr>
<tr>
<td>D5 H4</td>
<td>-1.425</td>
<td>-0.322</td>
<td>-1.043</td>
<td>-0.615</td>
<td>-0.655</td>
</tr>
<tr>
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<td>(1.075)</td>
<td>(1.066)</td>
<td>(1.132)</td>
<td>(1.566)</td>
<td>(0.914)</td>
</tr>
<tr>
<td>D5 H8</td>
<td>-2.688</td>
<td>-1.654</td>
<td>-1.562</td>
<td>-1.348</td>
<td>-1.390</td>
</tr>
<tr>
<td></td>
<td>(0.713)</td>
<td>(0.610)</td>
<td>(1.753)</td>
<td>(1.334)</td>
<td>(1.255)</td>
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</tbody>
</table>
Table 21: Mean pre-treatment scores (standard deviations) for compensatory tracking task – reaction time (msec) together with mean changes (standard deviations) from baseline for days 1 and 5 for all treatment conditions:

(Eba = ebastine, Trip = triprolidine)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eba 10mg</th>
<th>Eba 20mg</th>
<th>Eba 30mg</th>
<th>Trip 10mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D1 H0</strong></td>
<td>374.976 (45.311)</td>
<td>379.658 (49.757)</td>
<td>381.515 (50.676)</td>
<td>381.281 (45.622)</td>
<td>375.689 (40.460)</td>
</tr>
<tr>
<td><strong>D1 H2</strong></td>
<td>10.286 (13.289)</td>
<td>24.238 (18.627)</td>
<td>12.586 (23.673)</td>
<td>22.166 (24.398)</td>
<td>34.614 (17.114)</td>
</tr>
<tr>
<td><strong>D1 H4</strong></td>
<td>18.724 (16.514)</td>
<td>21.731 (41.767)</td>
<td>20.470 (30.574)</td>
<td>32.766 (17.533)</td>
<td>39.719 (25.774)</td>
</tr>
<tr>
<td><strong>D1 H8</strong></td>
<td>18.504 (17.854)</td>
<td>37.589 (39.603)</td>
<td>30.203 (37.248)</td>
<td>17.354 (26.515)</td>
<td>57.398 (46.783)</td>
</tr>
<tr>
<td><strong>D5 H2</strong></td>
<td>19.414 (20.853)</td>
<td>20.786 (22.893)</td>
<td>17.890 (39.513)</td>
<td>24.540 (52.433)</td>
<td>34.174 (30.980)</td>
</tr>
<tr>
<td><strong>D5 H4</strong></td>
<td>26.180 (26.558)</td>
<td>17.267 (32.256)</td>
<td>2.756 (53.997)</td>
<td>14.568 (27.806)</td>
<td>45.644 (34.004)</td>
</tr>
<tr>
<td><strong>D5 H8</strong></td>
<td>26.022 (15.737)</td>
<td>9.411 (24.534)</td>
<td>21.527 (51.607)</td>
<td>19.339 (33.812)</td>
<td>27.045 (30.927)</td>
</tr>
</tbody>
</table>
Table 22: Mean pre-treatment scores (standard deviations) for compensatory tracking task – tracking accuracy (rms) together with mean changes (standard deviations) from baseline for days 1 and 5 for all treatment conditions:
(Eba = ebastine, Trip = triprolidine)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eba 10mg</th>
<th>Eba 20mg</th>
<th>Eba 30mg</th>
<th>Trip 10mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 H0</td>
<td>5.770</td>
<td>6.515</td>
<td>5.609</td>
<td>6.272</td>
<td>6.028</td>
</tr>
<tr>
<td></td>
<td>(1.618)</td>
<td>(2.573)</td>
<td>(1.621)</td>
<td>(1.947)</td>
<td>(1.947)</td>
</tr>
<tr>
<td>D1 H2</td>
<td>-0.255</td>
<td>-0.429</td>
<td>0.210</td>
<td>-0.34</td>
<td>0.803</td>
</tr>
<tr>
<td></td>
<td>(0.413)</td>
<td>(0.648)</td>
<td>(0.600)</td>
<td>(0.356)</td>
<td>(0.741)</td>
</tr>
<tr>
<td>D1 H4</td>
<td>-0.118</td>
<td>-0.010</td>
<td>0.427</td>
<td>0.215</td>
<td>0.800</td>
</tr>
<tr>
<td></td>
<td>(0.530)</td>
<td>(1.159)</td>
<td>(0.800)</td>
<td>(0.458)</td>
<td>(1.744)</td>
</tr>
<tr>
<td>D1 H8</td>
<td>-0.095</td>
<td>0.304</td>
<td>0.027</td>
<td>0.184</td>
<td>1.318</td>
</tr>
<tr>
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<td>(0.447)</td>
<td>(2.163)</td>
<td>(0.123)</td>
<td>(0.851)</td>
<td>(4.000)</td>
</tr>
<tr>
<td>D5 H0</td>
<td>-0.526</td>
<td>-0.800</td>
<td>-0.683</td>
<td>-0.649</td>
<td>-0.683</td>
</tr>
<tr>
<td></td>
<td>(0.396)</td>
<td>(1.206)</td>
<td>(0.725)</td>
<td>(0.701)</td>
<td>(0.987)</td>
</tr>
<tr>
<td>D5 H2</td>
<td>-0.572</td>
<td>-1.273</td>
<td>-0.662</td>
<td>-0.560</td>
<td>-0.662</td>
</tr>
<tr>
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<td>(0.724)</td>
<td>(1.214)</td>
<td>(1.081)</td>
<td>(1.114)</td>
<td>(1.081)</td>
</tr>
<tr>
<td>D5 H4</td>
<td>-0.361</td>
<td>-1.307</td>
<td>-0.513</td>
<td>-0.349</td>
<td>-0.513</td>
</tr>
<tr>
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<td>(0.840)</td>
<td>(1.301)</td>
<td>(1.258)</td>
<td>(1.519)</td>
<td>(1.258)</td>
</tr>
<tr>
<td>D5 H8</td>
<td>-0.374</td>
<td>-1.012</td>
<td>-0.411</td>
<td>-0.533</td>
<td>-0.411</td>
</tr>
<tr>
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<td>(0.600)</td>
<td>(1.263)</td>
<td>(1.093)</td>
<td>(1.066)</td>
<td>(1.093)</td>
</tr>
</tbody>
</table>
Table 23: Mean pre-treatment scores (standard deviations) for short term memory scanning task (msec) together with mean changes (standard deviations) from baseline for days 1 and 5 for all treatment conditions:
(Eba = ebastine, Trip = tripolidine)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eba 10mg</th>
<th>Eba 20mg</th>
<th>Eba 30mg</th>
<th>Trip 10mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 H0</td>
<td>384.670 (60.320)</td>
<td>366.978 (45.933)</td>
<td>376.720 (56.265)</td>
<td>374.740 (63.506)</td>
<td>364.590 (43.252)</td>
</tr>
<tr>
<td>D1 H2</td>
<td>-7.80 (34.097)</td>
<td>-12.967 (21.168)</td>
<td>-2.480 (17.524)</td>
<td>-19.022 (34.896)</td>
<td>21.80 (32.746)</td>
</tr>
<tr>
<td>D1 H4</td>
<td>-21.690 (20.392)</td>
<td>5.456 (12.700)</td>
<td>-9.600 (18.740)</td>
<td>-10.40 (37.436)</td>
<td>24.310 (32.480)</td>
</tr>
<tr>
<td>D1 H8</td>
<td>-26.40 (30.480)</td>
<td>-5.189 (35.796)</td>
<td>-16.80 (14.117)</td>
<td>-8.389 (33.131)</td>
<td>23.410 (48.656)</td>
</tr>
<tr>
<td>D5 H0</td>
<td>-21.830 (32.787)</td>
<td>-9.533 (31.763)</td>
<td>-14.10 (17.835)</td>
<td>-27.044 (28.970)</td>
<td>-10.070 (16.829)</td>
</tr>
<tr>
<td>D5 H2</td>
<td>-25.270 (33.632)</td>
<td>1.178 (25.961)</td>
<td>-25.250 (41.454)</td>
<td>-14.789 (45.869)</td>
<td>-2.670 (924.913)</td>
</tr>
<tr>
<td>D5 H4</td>
<td>-23.440 (48.738)</td>
<td>-9.456 (41.384)</td>
<td>-13.720 (30.254)</td>
<td>-11.789 (69.587)</td>
<td>-4.290 (41.940)</td>
</tr>
<tr>
<td>D5 H8</td>
<td>-14.250 (47.077)</td>
<td>-16.189 (30.789)</td>
<td>-17.730 (33.986)</td>
<td>-21.778 (45.695)</td>
<td>-0.080 (23.147)</td>
</tr>
</tbody>
</table>
Table 24: Mean pre-treatment scores (standard deviations) for Line Analogue Rating Scales for Sedation (mm) together with mean changes (standard deviations) from baseline for days 1 and 5 for all treatment conditions:

(Eba = ebastine, Trip = tripolidine)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eba 10mg</th>
<th>Eba 20mg</th>
<th>Eba 30mg</th>
<th>Trip 10mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 H0</td>
<td>51.433 (3.422)</td>
<td>50.704 (0.853)</td>
<td>50.50 (0.563)</td>
<td>50.467 (0.40)</td>
<td>50.733 (1.181)</td>
</tr>
<tr>
<td>D1 H1</td>
<td>-0.533 (1.956)</td>
<td>-0.445 (1.054)</td>
<td>0.167 (0.833)</td>
<td>0.519 (0.918)</td>
<td>0.033 (0.433)</td>
</tr>
<tr>
<td>D1 H2</td>
<td>2.20 (3.560)</td>
<td>1.630 (4.476)</td>
<td>1.70 (2.904)</td>
<td>1.185 (2.085)</td>
<td>7.933 (6.335)</td>
</tr>
<tr>
<td>D1 H4</td>
<td>2.0 (3.827)</td>
<td>2.926 (3.295)</td>
<td>5.634 (6.165)</td>
<td>5.333 (4.879)</td>
<td>8.0 (7.309)</td>
</tr>
<tr>
<td>D1 H8</td>
<td>1.533 (2.227)</td>
<td>1.889 (3.236)</td>
<td>2.967 (3.035)</td>
<td>2.815 (3.225)</td>
<td>5.333 (5.871)</td>
</tr>
<tr>
<td>D5 H0</td>
<td>-0.367 (4.446)</td>
<td>-0.297 (0.576)</td>
<td>-0.10 (0.857)</td>
<td>-0.407 (1.538)</td>
<td>-0.30 (0.433)</td>
</tr>
<tr>
<td>D5 H1</td>
<td>-0.167 (2.237)</td>
<td>-0.370 (0.429)</td>
<td>0.033 (0.849)</td>
<td>1.371 (4.084)</td>
<td>-0.533 (1.045)</td>
</tr>
<tr>
<td>D5 H2</td>
<td>2.233 (4.669)</td>
<td>0.518 (1.744)</td>
<td>0.233 (1.086)</td>
<td>3.778 (5.482)</td>
<td>2.30 (4.664)</td>
</tr>
<tr>
<td>D5 H4</td>
<td>1.30 (3.542)</td>
<td>1.074 (2.083)</td>
<td>2.433 (4.101)</td>
<td>7.444 (9.383)</td>
<td>4.767 (4.782)</td>
</tr>
<tr>
<td>D5 H8</td>
<td>2.967 (4.212)</td>
<td>2.741 (6.415)</td>
<td>1.50 (2.372)</td>
<td>2.926 (4.011)</td>
<td>2.133 (4.385)</td>
</tr>
</tbody>
</table>
Table 25:  Mean pre-treatment scores (standard deviations) for Leeds Sleep Evaluation Questionnaire – Getting to Sleep (mm) together with mean changes (standard deviations) from baseline for all treatment conditions:
(Eba = ebastine, Trip = triprolidine)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eba 10mg</th>
<th>Eba 20mg</th>
<th>Eba 30mg</th>
<th>Trip 10mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 H0</td>
<td>50.967 (3.638)</td>
<td>51.333 (2.250)</td>
<td>49.833 (94.729)</td>
<td>52.10 (3.232)</td>
<td>51.833 (4.113)</td>
</tr>
<tr>
<td>D2 H0</td>
<td>1.233 (6.136)</td>
<td>4.333 (5.756)</td>
<td>7.60 (10.875)</td>
<td>12.592 (11.919)</td>
<td>11.10 (10.790)</td>
</tr>
<tr>
<td>D6 H0</td>
<td>4.867 (7.137)</td>
<td>8.222 (10.183)</td>
<td>2.0 (6.189)</td>
<td>10.741 (12.637)</td>
<td>4.967 (10.017)</td>
</tr>
</tbody>
</table>

Table 26:  Mean pre-treatment scores (standard deviations) for Leeds Sleep Evaluation Questionnaire – Quality of Sleep (mm) together with mean changes (standard deviations) from baseline for all treatment conditions:
(Eba = ebastine, Trip = triprolidine)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eba 10mg</th>
<th>Eba 20mg</th>
<th>Eba 30mg</th>
<th>Trip 10mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 H0</td>
<td>49.550 (3.643)</td>
<td>49.944 (1.877)</td>
<td>49.60 (5.389)</td>
<td>51.050 (3.798)</td>
<td>51.2 (3.551)</td>
</tr>
<tr>
<td>D2 H0</td>
<td>1.80 (13.437)</td>
<td>3.50 (11.993)</td>
<td>7.850 (11.354)</td>
<td>15.167 (13.762)</td>
<td>14.250 (12.758)</td>
</tr>
<tr>
<td>D6 H0</td>
<td>2.850 (4.172)</td>
<td>9.50 (11.232)</td>
<td>2.70 (7.467)</td>
<td>5.111 (15.663)</td>
<td>7.50 (12.307)</td>
</tr>
</tbody>
</table>
Experiment Seven

Table 27: Hamilton Anxiety Rating Scales: Mean values (Hz) and standard errors (s.e.) for the overall score, psychic and somatic scores for both treatment conditions:

*Intention to Treat with Last Value Carried Forward*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Visit</th>
<th>HAM-A Psychic</th>
<th>HAM-A Somatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDROXYZINE</td>
<td>1</td>
<td>9.90 (0.37)</td>
<td>15.48 (0.60)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6.14 (0.61)</td>
<td>7.55 (0.85)</td>
</tr>
<tr>
<td>LORAZEPAM</td>
<td>1</td>
<td>9.05 (0.37)</td>
<td>15.95 (0.68)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>7.08 (0.53)</td>
<td>10.87 (0.94)</td>
</tr>
</tbody>
</table>

Table 28: Cognitive Failures Questionnaire: Mean values together with standard errors (s.e.) with both treatments:

*Intention to Treat with Last Value Carried Forward*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Visit</th>
<th>Mean</th>
<th>s.e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyzine</td>
<td>1</td>
<td>51.404</td>
<td>2.33</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>50.024</td>
<td>2.44</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>45.929</td>
<td>2.60</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>45.833</td>
<td>2.63</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>44.595</td>
<td>2.52</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1</td>
<td>48.744</td>
<td>2.19</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>48.102</td>
<td>2.64</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>46.359</td>
<td>2.84</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>47.026</td>
<td>2.96</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>46.051</td>
<td>3.21</td>
</tr>
</tbody>
</table>
Table 29: Clinical Global Impressions – Cognitive Function: Mean change from baseline together with standard errors (s.e.) with both treatments:

*Intention to Treat with Last Value Carried Forward*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Visit</th>
<th>Mean</th>
<th>s.e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyzine</td>
<td>2</td>
<td>0.170</td>
<td>0.234</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.220</td>
<td>0.236</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.317</td>
<td>0.243</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.731</td>
<td>0.251</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2</td>
<td>-0.384</td>
<td>0.242</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-0.210</td>
<td>0.250</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>-0.256</td>
<td>0.259</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>-0.333</td>
<td>0.280</td>
</tr>
</tbody>
</table>

Table 30: Clinical Global Impressions – Quality of Sleep: Mean change from baseline together with standard errors (s.e.) with both treatments:

*Intention to Treat with Last Value Carried Forward*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Visit</th>
<th>Mean</th>
<th>s.e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyzine</td>
<td>2</td>
<td>1.488</td>
<td>0.229</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.561</td>
<td>0.229</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1.537</td>
<td>0.281</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1.683</td>
<td>0.284</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2</td>
<td>1.513</td>
<td>0.294</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.605</td>
<td>0.281</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1.230</td>
<td>0.303</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1.230</td>
<td>0.317</td>
</tr>
</tbody>
</table>
Table 31: Critical Flicker Fusion: Mean Values (Hz) together with standard errors for both treatment conditions:

*Intention to Treat with Last Value Carried Forward*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Visit</th>
<th>Mean</th>
<th>s.e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyzine</td>
<td>1</td>
<td>30.285</td>
<td>0.434</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>29.601</td>
<td>0.466</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>29.432</td>
<td>0.511</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>30.198</td>
<td>0.505</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>29.888</td>
<td>0.508</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1</td>
<td>30.553</td>
<td>0.547</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>30.745</td>
<td>0.550</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>30.682</td>
<td>0.462</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>30.792</td>
<td>0.488</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>30.953</td>
<td>0.494</td>
</tr>
</tbody>
</table>

Table 33: Leeds Sleep Evaluation Questionnaire – Awakening from Sleep: Mean Values together with standard errors (s.e.) for both treatments:

(GTS = Getting to Sleep, QOS = Quality of Sleep, AFS = Awakening from Sleep)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Visit</th>
<th>GTS</th>
<th>QOS</th>
<th>AFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyzine</td>
<td>2</td>
<td>32.61 (2.50)</td>
<td>34.26 (3.04)</td>
<td>49.81 (2.20)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>35.73 (1.89)</td>
<td>32.91 (2.66)</td>
<td>45.43 (2.32)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>34.79 (2.04)</td>
<td>33.61 (2.79)</td>
<td>45.06 (2.14)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>32.86 (2.11)</td>
<td>32.36 (2.85)</td>
<td>42.98 (2.78)</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2</td>
<td>27.16 (2.56)</td>
<td>33.93 (2.82)</td>
<td>57.01 (3.67)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>28.16 (2.45)</td>
<td>31.11 (2.88)</td>
<td>53.59 (4.19)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>30.84 (3.01)</td>
<td>36.70 (3.33)</td>
<td>53.85 (4.01)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>33.28 (3.24)</td>
<td>35.89 (3.48)</td>
<td>53.55 (4.30)</td>
</tr>
</tbody>
</table>