Antihistamines and Driving-Related Behavior

A Review of the Evidence for Impairment

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drug, dose, dosing schedule (i.e., sing	le versus repeated) and H	1-antagonist generation	as well as by beha	avioral area or		
subjective measure. For each H1-anta	agonist generation, five d	rugs were evaluated: c	hlorpheniramine, c	elemastine,		
diphenhydramine, hydroxyzine and tr	ipolidine for the 1 st -gener	ation, and astemizole, c	etirizine, fexofena	dine, loratadine and		
terfenadine for the 2 nd -generation. It	was concluded that:					
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1. There is some slight, but amb	biguous, evidence from e	pidemiological studies of	of a connection bet	ween antihistamine		
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impairment, some methods a	nd behavioral domains an	re more sensitive to the	effects of antihista	mines. Future		
studies of antihistamines, the	refore, must utilize the m	ost methodologically-s	ound techniques so) as to permit a		
better comparison between d	ifferent drugs.		-	-		
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			Period: September 2000-February 2003 14. Sponsoring Agency Code driving-related skills was conducted. After ations were found to meet criteria for ng indexed, and summarized, by specific eration as well as by behavioral area or ted: chlorpheniramine, clemastine, izole, cetirizine, fexofenadine, loratadine and tudies of a connection between antihistamine arily when use of only 1st-generation (but not led. the 1 st -generation antihistamines produce symptoms of sedation. pharmaceutical industry in reducing potential even the 2 nd - generation drugs, may cause some individuals. is considerable variation in objective us, there clearly are drugs that are to be ated performance impairment. les for investigating driving-related to the effects of antihistamines. Future cally-sound techniques so as to permit a tement is available to the U.S. public through the ical Information Service ginia 22161			
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ANTIHISTAMINES AND DRIVING-RELATED BEHAVIOR: A REVIEW OF THE EVIDENCE FOR IMPAIRMENT BY FIRST- VERSUS SECOND-GENERATION H₁-ANTAGONISTS

Herbert Moskowitz, Ph.D. and Candace Jeavons Wilkinson, Ph.D.

1. INTRODUCTION

1.1 Statement of The Problem

The single largest contributing factor in fatal motor vehicle crashes in the United States is alcohol-induced impairment (AMA Council on Scientific Affairs, 1986). While this has been the case for many years, there also has been an increasing awareness of the traffic safety risks due to the behavioral toxicity of drugs other than alcohol. These include not only illicit drugs, such as cocaine and marijuana, but also medicinal drugs available by prescription or over the counter. In particular, the widespread use of antihistamines (i.e., histamine H₁-receptor antagonists, or H₁-antagonists for short) presents a particular focus for concern since the 1stgeneration H₁-antagonists are well recognized for often causing sedation and central nervous system (CNS) dysfunction which can jeopardize safe driving. Moreover, these drugs also have additive effects with alcohol and other CNS depressants. An awareness of such safety risks actually was known more than 50 years ago with the initial introduction of clinically-useful H₁antagonists. For example, in the same year that it received marketing approval by the Food and Drug Administration (FDA), 1946, diphenhydramine (Benadryl) was implicated as a contributing cause of a workplace accident involving impaired driving of a platform cargo truck (Slater & Francis, 1946). And more recently, a study of the association of 3,394 work-related injuries and prior usage of medication (as determined from actual pharmacy records) found a statistically significantly increased risk of injury (odds ratio = 1.5) among users of sedating antihistamines (Gilmore et al., 1996).

Currently, there are more than 60 antihistamines available for oral administration (Maibach, 1988) and many of these are freely available without prescription (i.e., over-the-counter). Commonly, antihistamines are the primary active ingredients in the myriad of cold and flu preparations. Antihistamines also are used individually as 1st-line treatment for the prevalent allergic conditions of rhinitis and chronic urticaria. Other treatment indications for these H₁-antagonists include motion sickness, vertigo associated with Meniere's disease, vascular headaches, and tremors of Parkinsonism. These drugs also are used for their antipruritic (i.e., for itching), antiemetic (i.e., for nausea), antitussive (i.e., for cough), anxiolytic (i.e., for anxiety) and sedative effects (i.e., for insomnia). Such widespread use underscores the increasing scope of the potential safety risks associated with their use by the driving population.

Notably, most states have enacted laws which prohibit driving under the influence of any drug that impairs driving (U.S. DOT, 1996); this, of course, would include sedating antihistamines that disrupt alertness, perception and performance. At the federal level, recent reports have focused on safety standards relating to the use of antihistamines both by workers in the transportation industry as well as by the driving public (cf. Office of the Assistant Secretary for Transportation Policy, Office of Environment, Energy and Safety, 1998). In brief, there have been increasing

traffic safety concerns about the possible detrimental effects of medicinal drugs including the widely used antihistamines. But what evidence is there? The answer requires an examination of the problem from several perspectives. As suggested in an early review of alcohol, drugs and traffic safety (Smiley & Brookhuis, 1987; p. 83), "epidemiological studies, laboratory tests of driving-related skills, simulator studies and on-road studies each provide a vital part of the evidence establishing the role of any given substance to traffic safety." The current review will focus on each of these perspectives, but will only provide a brief summary below of the epidemiological data and its limitations.

1.2 Limitations of Epidemiological Data

The scientific literature regarding impairment of driving-related skills performance by antihistamines consists primarily of experimental studies. These are studies where subjects or patients are administered known doses of antihistamines and then their performance is compared with that under placebo treatment or under comparable antihistamines. The emphasis on experimental studies in this report is due to the paucity of epidemiological studies and the difficulties in interpreting their results.

One of the earliest epidemiological studies of drugs and traffic safety was performed by Skegg, et al. (1979). The authors reviewed the prescription history for more than 43,000 patients over a two-year period. During that period, 57 people in the sample were injured or killed while driving either an automobile, motorcycle or bicycle. For these victims, the drugs prescribed in the preceding three months were compared with those in 1,425 control patients who were selected from the overall sample population as having the same gender, age and prescribing physician. Three of the crash-involved drivers, or 5.3% of the crash group, had been prescribed an antihistamine. Forty-three control drivers, or 3.0% of the control group, had received an antihistamine prescription. The relative risk is 1.8, but obviously this is not significant since it is based on only three injured drivers. It should be noted that in this study, tranquilizers and sedatives as a class showed a statistically significant, relative risk of 5.2.

Ray, et al. (1992) performed a similar study examining the relationship between psychoactive drugs and the risk of a motor vehicle injury crash in elderly drivers in a medicaid program. The advantage of using elderly drivers, over age 65, is that objective data were obtained from the Tennessee medicaid program regarding prescription drug use. Only drivers involved in an injury crash were included in the study, because it was believed that collisions involving only property damage are substantially under-reported and therefore would be less reliable. More than 16,000 people were in the study group which reported 495 injury crashes in a four-year period. Considerable information was available, both from the medical records and the drivers license records. The study employed a multiple regression analysis which controlled for many of these factors. The relative risk of involvement in an injury crash was 1.2 for current antihistamine use. The 95% confidence interval ranged from a relative risk of 0.6 to 2.4. Again there appears to be only a trend (i.e., statistically insignificant effect) to suggest that the use of antihistamines actually results in an increased crash rate. As noted, this study examined an elderly population. Whether or not an interaction exists between the effects of antihistamine use and age, however, has not been determined.

In a 1992 study by Terhune, et al., blood samples were collected from 1,882 fatally injured drivers from seven states during fourteen months in1990 and 1991. The prevalence of antihistamines in body fluid samples from these drivers was 0.6%. In order to determine the significance of the presence of antihistamines, since no comparable control group was available, the authors used a culpability/responsibility analysis which relied on expert raters

utilizing police reports of the crash to assign responsibility. Only six drivers had antihistamine present and the responsibility rate was not explicitly stated by the authors, except to indicate that it was not significant.

A 1993 study by Crouch, et al., of 168 fatally injured truck drivers failed to uncover any drivers with an antihistamine present. In contrast, in a study by Warren, et al. (1981) of 768 fatally injured drivers from Ontario, Canada in 1978 to 1979, nine drivers were found to be using antihistamines. A culpability rate analysis indicated a 1.5 culpability rate.

It should be noted that there is considerable difficulty inherent in the attempts to use culpability analysis to compensate for the difficulty of obtaining adequate control groups. Shinar, et al. (1983) compared traffic crash reports by the police with those generated by a university-based investigational team, for example, and found that the police reports frequently omitted important information especially with regard to human factors. In addition, Waller (1982) criticized epidemiological studies of drug effects in driving which relied on culpability/ responsibility analysis because they failed to control for important determinants of driving crash rates such as time and place of collision and characteristics of the drivers. Waller compared studies using culpability analysis with studies utilizing the data of the Grand Rapids alcohol study (Borkenstein, et al., 1964). The Grand Rapids study provided information regarding covariates from both the crash-involved and control groups. This enabled researchers examining the Grand Rapids findings to extract the specific effect of alcohol on crash probability from the influence of variables such as age, gender, drinking practices, etc., which all contribute to an overall crash probability.

It would appear that epidemiological studies involving known populations with verifiable drug use are more likely to produce secure information than epidemiological studies that begin with drivers injured or killed on the road. These latter types of epidemiological studies have no comparable control groups even were we to rush to the scene of crashes, such as was done in the Grand Rapids study. While the Grand Rapids study was able to obtain breath alcohol samples from both crash and control drivers, efforts to obtain blood or urine samples from drivers have been notably unsuccessful. Moreover, even if we had blood samples from both groups, crash and control drivers, interpreting the behavioral implications of plasma drug levels is extremely difficult, as others have already elucidated in detail (e.g., Chesher, 1985).

We typically know the most about drugs detected in fatally injured drivers. However, we also know from studies on alcohol that the probability of being involved in a fatal crash is highly dependent on the blood alcohol concentration (BAC). It is not merely the probability of being involved in a crash that increases with BAC level; but given that you are involved in a crash, there is an additional interacting factor that the probability of death increases with BAC. There is nothing about the studies on antihistamines, however, that would suggest that the magnitude of behavioral effects are comparable with those associated with moderate to higher BAC levels. Thus, the lower magnitude of impairment by the antihistamines would be unlikely to show up in studies of fatal crashes unless the numbers were huge.

We conclude that the epidemiological evidence obtained from studies where 1st-generation antihistamines were commonly used suggests a trend toward some impairment, but not of great magnitude compared with the increased risks associated with alcohol. In summary, given the limitations of epidemiological studies, we believe that experimental studies provide the fundamental method for investigating the direct relationship between a given medication dose and driving efficiency in actual practice. That is, our evaluation of the effects of antihistamines on driving must rest primarily on experimental laboratory studies where we have known dose levels, placebo controls and established experimental response measures. As a background for evaluating such experimental studies of the effects of antihistamines on driving-related performance, a brief description of the clinical pharmacology of the H₁-antagonists is presented next.

1.3 Clinical Pharmacology & Issue of Drug Choice

Although the exact mechanisms of action for the histamine H_1 -receptor antagonists remain unknown, the role of histamine as a neurotransmitter is now firmly established. Histaminergic pathways are widespread in the CNS and appear to be related to mechanisms that support alertness and vigilance during the wakeful state and the balance between wakefulness and slow-wave activity during sleep (Nicholson et al. 1985). Histamine, an endogenous substance first recognized in 1927, has strong vasodepressant and smooth muscle stimulant actions (Garrison, 1990). Considerable research since then has elucidated histamine's roles in mediating the immediate allergic response [via H_1 -receptors], regulating gastric acid secretion [via H_2 -receptors] and possibly functioning as a neurotransmitter [via H_3 -receptors] (White, 1990). The focus of the current review is limited to the H_1 -receptor antagonists.

The H₁-antagonists bind to peripheral and central H₁-receptors and thereby block or, more accurately, compete with histamine's effects. That is, the effectiveness of the H₁-antagonist medications is related to the relative concentrations of histamine and its antagonist at the receptor site: an adequately high and frequent enough dosage of the drug is required in order to maintain sufficient concentrations to compete with histamine. An effective dose, however, often is associated with deleterious side effects which include, at least for the classical or 1st-generation drugs, sedation and anticholinergic effects such as dry mouth, nose or throat. The sedative side effects of the 1st-generation H₁-antagonists are due to their affinity for central H₁-receptors and their liposolubility which enables them to cross the blood-brain barrier. The anticholinergic and other adverse side effects arise from the 1st-generation H₁-antagonists' affinity for muscarinic anticholinergic, "-adrenergic, and serotonin receptors.

Newer, 2nd-generation H₁-antagonists have been developed in the past decade. Their availability provides allergy patients the choice of new drugs which have little or no side effects such as the sedation and psychomotor impairment often found with the 1st-generation drugs. The 2nd-generation drugs penetrate poorly into the CNS and so are *relatively* non-sedating, in contrast to the 1st-generation drugs which readily penetrate the blood-brain barrier. Also, the newer drugs have little or no affinity for muscarinic cholinergic, " -adrenergic, and serotonin receptors. This is in contrast to the 1st-generation drugs which do possess such activity. These factors may contribute to the relative lack of adverse CNS or peripheral effects by the 2nd-generation drugs (Simons, 1994). Of note, in the 2nd-generation drugs, there appears to some difference in potential side effects associated with the piperidine class (e.g., astemizole, fexofenadine, loratadine, and terfenadine) versus the piperazine class (e.g., cetirizine).

In sum, the pharmacodynamics and side effects profiles of the 2nd-generation H₁-antagonists suggest that these newer drugs offer a safety advantage particularly for patients who drive, pilot

aircraft or operate machinery and must avoid the sedation and impaired performance which are commonly found with the 1st-generation drugs. Prior reviews of the experimental studies which have examined the effects of H₁-antagonists on performance measures from laboratory tests, driving simulators and on-road driving generally have concluded that the 2nd-generation drugs do pose little or no risk to safe driving. The major prior reviews of those findings are summarized below.

1.4 Prior Reviews of H₁-antagonists

Starmer (1985) provided the earliest review of the evidence concerning antihistamines and traffic safety. He concluded that experimental studies found sedation, impaired performance skills and additive effects with alcohol and other CNS-depressant drugs to be prominent within the heterogenous group of 1^{st} -generation H₁-antagonists. He noted, however, that these drugs were seldom identified as causative factors in traffic crashes, possibly due to inadequate reporting. Finally, the several newer, or 2^{nd} -generation H₁-antagonists available for study at that time all appeared to have little CNS effect and so presented less risk of impaired driving.

More recent reviews have included those by Rombaut & Hindmarch (1994), Hindmarch (1995), and Adelsberg (1997). The most comprehensive evaluation, however, is provided by Simons (1994) who reviewed the comparative safety of the 1st- and 2nd-generation H₁-antagonists in terms of CNS function as well as for cardiovascular adverse effects (specifically seen with some of the newer drugs). Simons, as other reviewers, concluded that the 2nd-generation H₁- antagonists are *relatively* devoid of sedation and CNS impairment, and so they clearly do provide a better "benefit-risk ratio" than do the 1st-generation drugs. Nonetheless, most reviewers also noted that the findings for cetirizine, a 2nd-generation drug, were rather mixed, with some reports of sedation and performance impairment on laboratory tasks as well as on actual driving. The prior reviews also emphasized the difficulty in evaluating the safety profiles of a given drug since the doses, tasks and measures across the studies varied widely.

1.5 Focus of Current Review

Over five years have passed since the most comprehensive review of antihistamines' effects was published (Simons, 1994). Thus, the present review was undertaken to provide a current status of the experimental evidence for impairment of driving-related skills by 1st- versus 2nd-generation H₁-antagonists. Importantly, many more studies of the 2nd-generation drugs have been published during this time. Hopefully, these newer studies have employed refined methods and more sensitive measures to detect drug-induced sedation and impairment. Also of note, Simons' (1994) review included approximately 50 controlled studies which compared drugs from the two generations in a single design. However, there are many more studies of the H₁-antagonists if one also considers experiments which only examined drugs from one generation or the other. For example, the 1st-generation H₁-antagonists often are included as a positive control drug in studies of various drugs other than the antihistamines. Also, some study designs test only a single drug, from the 1st- or 2nd-generation, against a placebo control.

The purpose of the current review is to summarize and evaluate the results of experimental studies measuring the effects of 1^{st} - and/or 2^{nd} -generation H₁-antagonists on behavioral and cognitive performance skills relevant for driving. Measures of subjective sedation also are evaluated but only if they were part of a study primarily investigating behavioral or cognitive effects. That is, this review did not include clinical trials which were limited only to reported

adverse effects or subjective ratings. Alcohol's effects on driving-related performance have been studied extensively and can be used as benchmark to evaluate the traffic safety profile of medicinal drugs. Thus, for consistency and comparison, the current review organized the performance measures generally within the same behavioral categories as employed in the first author's prior reviews on alcohol's driving-related effects (Moskowitz & Robinson, 1988; Moskowitz and Fiorentino, 2000). Finally, studies investigating acute and chronic doses were considered for this review, whereas studies of drug-alcohol (and drug-drug) interactions were not included since such studies were more limited in number.

2. METHOD

Computer-assisted searches of bibliographical data bases were conducted to identify scientific publications for the initial review. Specifically, MEDLINE and related search engines were used to identify well-designed human studies investigating the behavioral, cognitive and sedative effects of antihistamines. Search terms included: antihistamines, H1-antagonists, psychomotor performance, driving, performance impairment, and cognitive effects. Publications through the end of 1998 were included; no particular date limit was set regarding earlier publications, although it should be noted that MEDLINE typically does not include publications prior to 1966. This primary computer-assisted search was supplemented by review of the references cited in the retrieved publications as well as consideration of reports of pertinent studies known to the authors. Therefore, in addition to published journal articles, some abstracts, proceedings, and reports of conference presentations also were included. Although an extensive literature search was conducted, the results cannot be viewed as exhaustive.

The titles (or abstracts) of the identified references were evaluated for initial inclusion according to the following criteria: the article (or detailed abstract) was available in English, the study tested healthy human subjects (or allergy patients), measures included driving-related performance tasks, antihistamines were administered in an experimental setting, a placebo control treatment was included, and statistical tests compared the treatment(s) to placebo. All publications appearing to meet these initial criteria were indexed as the master reference set and copies of the articles were sought for intensive review. This master set included 386 references selected from more than 500 titles/abstracts reviewed in the initial focused search. Of the 386 references identified, 256 were excluded from the intensive review and analysis for the following reasons, as shown in Table 1 below:

EX#	TABLE 1. REASONS FOR STUDY EXCLUSION:	no.	%
1	NOT in English; OR English summary lacks sufficient detail to review	14	5.5
	NOT adult subjects; OR not healthy volunteers or allergy patients; Excluded other clinical patients (e.g., abstinent alcoholics, depressed patients)		
	NO driving-related tasks used in the experiment; (but coded subjective sedation only from studies which tested at least one behavioral/cognitive measure)	42	16.4
4	NO key drugs included (per top 5 for each H1-antagonist generation; see lists)	67	26.2
	Inadequate methodology (need at least Placebo; best if +Control also included) OR statistical tests only used baseline change, not comparison with Placebo		3.9
	NOT an experiment; e.g., Review paper with no new experiments reported; or Review of pharmacology or clinical effects, epidemiology, or case report, etc.		31.2
	Prior published data; (Note: included earliest publication unless later paper provided a more detailed report of the findings)	17	6.6
8	Unable to obtain copy of article for detailed review	13	5.1
9	Copy obtained, but article had insufficient detail to allow review of criteria	3	1.2
	TOTAL: 256		

The remaining 130 publications which met all inclusion criteria were then subjected to intensive review and the findings were coded and entered into the data base for summary and analysis. The complete citations for this final set of 130 publications appear as REFERENCE LIST B at the end of this report. Originally, 132 articles were deemed appropriate for the intensive review and so they are indexed in the data base (and in all appended Tables and listings) as Reference

Numbers 1-132 in alphabetical order by first author. Subsequently, four of these articles were excluded from the review set (Ref# 10, 52, 72, and 118) and two additional publications (published in late 1998) were identified and added to the data base. However, to avoid major recoding and reorganization of the data base, the two added articles simply were indexed as Reference #133 (Comer et al., 1998) and #134 (Scavone et al., 1998). As such, they appear at the end of the data base and reference list, rather than in alphabetical order.

A complete listing of the individual studies, with impairment findings grouped according to the behavioral skill categories (discussed in detail below), is presented in Appendix A. In addition, for each task category, an overall summary table of "Skills performance impairment as a function of antihistamine (Drug/Dose), task category and dosing (Acute/Repeated)" was generated to present the counts of YES and NO for significant impairment. An example of such a "YES/NO Counts" table is presented in Appendix B. The tables in Appendix A and B also summarize the findings by drug generation as a class.

Details of the data base coding system can be found in an example of one of the individual Study Summary Sheets which were generated for all 130 articles (see Appendix C for an example). In brief, each article was reviewed and the information for the Citation, Method, and Results of each reported study was entered in the data base. Of note, seven publications reported more than one experiment; in these cases, the data base includes the single Citation, but separate Methods and Results sections for each of the studies which are indexed by the single Reference number plus a letter; (e.g., Reference #18 reports two separate studies: these are indexed as Reference #18A and #18B). The 130 publications reflect a total of 138 separate studies; these are included in the data base for this review.

The results from each study were coded, at the level of drug dose and task measure, for evidence of significant impairment, i.e., YES or NO. With few exceptions, "significant" means that the study reported a statistical test of the given drug's dose versus placebo at p < 0.05.

Nearly 40 different antihistamines were represented in the master data set of publications which were identified in the initial, focused literature search. In many cases, only a few studies (and sometimes only one study) examined a given drug, and many of the drugs are (were) only available in Europe. Consequently, in order to ensure an adequate sample of studies for this review, and to be relevant to the medications available to the U.S. population of drivers, we decided to focus only on the five most widely prescribed and/or studied drugs from each generation. These 10 drugs are described in detail in Table 2, as shown on the next page.

A table which lists all of the studies in this review, presented with the YES/NO codes across all 10 drugs, is presented in Appendix D. This listing provides a concise overview of the specific drugs examined in a given study. Of note, the majority of studies focused on only one of the 10 drugs. Only 12 studies involved a comparison of two different 2nd-generation drugs, and only a single study (Simons, 1996) examined a group of 2nd-generation drugs in comparison to placebo and to a 1st-generation antihistamine as the positive control (e.g, diphenhydramine).

TABLE 2.THE TEN DRUGS SELECTED FOR REVIEW

Code	generic name:	Trade name:	Drug CLASS	Indicated DOSE	Tmax	Steady State
	generic name.		Diug CLASS			_
D1	chlorpheniramine	Chlor-Trimeton	Alkylamines	4 mg tid, qid	2-6 hr	T1/2: 20-24hr
D2	clemastine	Tavist	Ethanolamines	1.34 bid - 2.68 tid	2-4 hr	
D3	diphenhydramine	Benadryl	Ethanolamines	25-50 mg tid,qid	2-4 hr	T1/2: 8 hr
D4	hydroxyzine	Atarax	Piperazines	25 mg tid, qid	2-3 hr	T1/2: 29 hr
					~ 2 hr	T1/2: ~2 hr
	tripolidine There are six generally reco antihistamines: Alkylamine Phenothiazines, Piperazine	es, Ethanolamines, s, and Piperidines.	Ethylenediamines			ed release
Note:	There are six generally reco antihistamines: Alkylamine	ognized chemical c es, Ethanolamines, s, and Piperidines.	lasses of Ethylenediamines	or 10 mg SR	sustain	ed release
Note:	There are six generally reco antihistamines: Alkylamine Phenothiazines, Piperazine	ognized chemical c s, Ethanolamines, s, and Piperidines.	lasses of Ethylenediamines gonists:	or 10 mg SR SR = : S, T1/2 =	sustain = Half-I	ed release ife
Note: Seco Code	There are six generally reco antihistamines: Alkylamine Phenothiazines, Piperazine ond-generation H1-r generic name:	ognized chemical c es, Ethanolamines, s, and Piperidines. eceptor antag	lasses of Ethylenediamines gonists: Drug CLASS	or 10 mg SR SR = : S, T1/2 =	sustain = Half-I <u>Tmax</u>	ed release ife <u>Steady State</u>
Note: Seco Code N1	There are six generally reco antihistamines: Alkylamine Phenothiazines, Piperazine ond-generation H1-r generic name: astemizole	pgnized chemical c es, Ethanolamines, s, and Piperidines. eceptor antag Trade name: Hismanal	lasses of Ethylenediamines gonists: <u>Drug CLASS</u> Piperidines	or 10 mg SR SR = 1 S, T1/2 = Indicated DOSE 10 mg qd	sustain = Half-I <u>Tmax</u> 1 hr	ed release ife <u>Steady State</u> 6-9 days
Note: Seco Code N1 N2	There are six generally reco antihistamines: Alkylamine Phenothiazines, Piperazine ond-generation H1-r generic name: astemizole cetirizine	pgnized chemical c es, Ethanolamines, s, and Piperidines. eceptor antag <u>Trade name:</u> Hismanal Zyrtec	lasses of Ethylenediamines gonists: Drug CLASS Piperidines Piperazines	or 10 mg SR SR = 1 S, T1/2 = Indicated DOSE 10 mg qd 10 mg qd, bid	sustain = Half-I <u>Tmax</u> 1 hr 1 hr	ed release ife <u>Steady State</u> 6-9 days T1/2: 7-11 hr

Each drug was indexed in the data base and in all generated figures and listings by a drug code number: D1-D5 and N1-N5, respectively, reflect the five drugs in the 1st-, and 2nd-, generations. Only one study of fexofenadine's effects on driving-related behavior has been published to date (i.e., through the end of 1998 in this review). Its inclusion in this review, however, is warranted by its current status as one of the most widely prescribed antihistamines and the fact that its chemical structure is identical to terfenadine's active metabolite, except that fexofenadine is the hydrochloride salt. Terfenadine was taken off the market in early 1998 after increased reports of cardiovascular adverse effects. Nonetheless, as the parent drug to fexofenadine, the many studies of terfenadine are included in this review for their continued relevance for understanding the drug mechanism and impairment effects of the 2nd generation drugs. In addition, astemizole recently was removed from the market due to safety concerns.

In addition to the drug coding, the results for each study were entered in the data base according to the planned analysis of the **ten behavioral skill categories**, as shown in Table 3 below. In addition, as noted earlier, **subjective measures of sedation** were analyzed if the study also had tested at least one behavioral or cognitive measure.

Table 3.NUMBER OF STUDIES AND TEST FINDINGS FOR EACH SKILL CATEGORY
AND SUBJECTIVE SEDATION: ACUTE (A) AND REPEATED (R) DOSING

SC	SKILL CATEGORY	Examples of Measures Tested		Number of STUDIES		Number of Findings	
#		(with specific sub codes shown)	Α	R	Α	R	
1	DRIVING & PILOTING	1R: on road, 1C: closed course, 1S: simulator	17	14	55	28	
2	PSYCHOMOTOR	2B: body sway, balance, hand steadiness, 2D: dexterity, 2T: finger tapping; 2: all others	35	9	70	17	
3	PERCEPTION	time perception, visual search tasks	14	7	26	13	
4	VISUAL FUNCTIONS	4: visual functions, 4C: critical flicker fusion	34	10	83	16	
5	COGNITIVE TASKS	5D: digit symbol substitution test, 5M: memory tasks, 5T: trail-making, 5: all other cognitive tasks	63	20	201	61	
6	DIVIDED ATTENTION	typically visual search performed with tracking task	28	8	52	14	
7	VIGILANCE	sustained attention; lengthy monotonous tasks	25	12	46	24	
8	TRACKING	8Cr: critical or adaptive tracking, 8: pursuit, compensatory, or unspecified tracking tasks	39	10	80	23	
9	REACTION TIME	9S: simple RT, 9C: complex RT	50	20	98	44	
10	PHYSIOLOGICAL	10: EEG, ERP, 10M: Multiple Sleep Latency Test	23	14	56	33	
99	Subjective Sedation	Visual analogue scales, Stanford Sleepiness Scale	85	29	171	50	
(from n = 135 studies of Acute and/or Repeated Doses) TOTALS:			113	47	938	323	

Note: **A = ACUTE Doses; R = REPEATED Doses**; (excluded 3 studies with only Residual effects). Many studies tested more than one skill category, measure, drug, and dose level and schedule.

It should be noted that the terms "**test**" or "**finding**" are used interchangeably in this report to describe the **unit of data analysis** for this comprehensive review of 138 studies. A given study, for example, may have evaluated several drugs and doses, both acute and repeated dosing schedules, and included multiple behavioral measures and subjective measures. The resultant total number of specific "tests" or "findings" from that single study, therefore, would be the product of multiplying all the levels for each factor studied. Thus, as shown in the table above, there is a total of 1,261 test findings; obviously this number is much greater than the total number of studies included in the review. Also, the number of findings for repeated dosing was rather limited (n=323) compared to the greater number for acute dosing (n=938).

The decision for classifying the many performance measures into 10 behavioral categories is admittedly somewhat arbitrary. Prior reviewers also have noted the difficulties inherent in this process of assigning a given task to a specific category (e.g., Adelsberg, 1997; Rombaut & Hindmarch, 1994), but most concur with the general areas of actual driving, simulated driving, various psychomotor skills, sensorimotor tasks, cognitive effects, and subjective measures of sedation. In order to evaluate more precisely the drug effects on the wide variety of measures, we also included sub codes in an effort to restrict the variability of findings within a given area. Specific task names and the individual response measures can be found in the detailed tables which list the impairment results by study (see Appendix A).

3. RESULTS

There is considerable complexity in the task of evaluating 10 drugs for evidence of subjective sedation and objective impairment of a variety of performance measures grouped into 10 specific behavioral categories. Moreover, each drug has been studied across multiple dose levels as well as for acute versus chronic dosing schedules. Therefore, the results of this review are organized into the following major sections below: Overall impairment, Impairment by individual drugs, and Impairment by behavioral categories and subjective sedation.

3.1. Overall Impairment

3.1.1. Impairment Findings by Study for each Drug(Figure 1 and Appendix D)

Of the 135 studies which examined acute or repeated dosing (or both) of any of the 10 key drugs, 120 tested 1st generation drugs and 87 tested 2nd generation drugs. (Since many studies evaluated several drugs, often from both generations, the numbers overlap. Also, the three studies which only evaluated residual effects are excluded from the data summaries.) As can be seen in Figure 1, the most frequently studied drugs for the 1st and 2nd generations, respectively, were diphenhydramine (49 of 120 studies, or 41%) and terfenadine (37 of 87 studies, or 43%). As noted earlier, only a single study of fexofenadine had been published as of the 12/98 cutoff date (i.e. for the published articles of the studies) for this review. Thus, those findings must be viewed cautiously until additional studies are reported to determine if those findings generalize or not to other samples of subjects and measures.

First, we considered the category of <u>studies</u>, (as distinguished from the number of behavioral task *measures* of which typically there are several per study), which tested *either acute or chronic doses* and found *any evidence* of statistically significant impairment (relative to a placebo control treatment) of *either objective or subjective measures*. We found that 88% (106 of 120) of the studies of the 1st generation drugs found impairment as compared to 22% (19 of 87) of the studies of the 2nd generation drugs. And as expected, for each of the five drugs within each generation, more studies found impairment than not for the 1st generation drugs, whereas the majority of the studies of the 2nd generation drugs found no significant impairment. Nonetheless, there is considerable variability for the findings of significant impairment within each drug generation. Specifically, the significant findings range from 69% (11 of 16 studies of clemastine) to 95% (18 of 19 studies of chlorpheniramine) for the 1st generation drugs, and from 9% (1 of 11 studies of astemizole) to 35% (7 of 20 studies of cetirizine) for the 2nd generation drugs. This excludes, of course, the single study of fexofenadine which did find some evidence of impairment. Given this wide variability, a more focused analysis is needed.

3.1.2. Impairment Findings as a function of Objective/Subjective Measures, Drug Generation, and Dosing Schedule (Acute versus Repeated) (Figure 2)

Since the overall impairment findings by study obviously reflect considerable variation in terms of objective versus subjective measures as well as acute versus repeated dosing, the next step was to summarize the findings as a function of these key factors. Moreover, instead of

evaluating impairment at the study level, all subsequent analyses focused on the findings for the individual and specific *"behavioral task measures"* which, as described earlier, present a finer level of analysis for this comparative review of 1st versus 2nd generation antihistamines. That is, for a given study, the individual test findings reflect the outcome of the statistical significance test for impairment for a given drug, at a given dose and dosing schedule, and for a specific measure within one of the 10 behavioral categories or for subjective sedation.

Considering first the *acute dose findings* (Figure 2), the 1st generation drugs as a group were found more often than not to be impairing in both objective and subjective measures. The 2nd generation drugs, in contrast, showed substantially fewer findings of impairment for either objective or subjective measures.

Relative to the acute effects, the *repeated dose findings* for both drug generations generally show less impairment, at least for the objective measures, as might be expected given that tolerance may develop with chronic dosing. For the subjective measures, however, the 1st generation drugs still have more findings of significant sedation than not even after repeated dosing. In contrast, none of the findings for the 2nd generation drugs indicate any significant sedation after repeated doses. Again, there is wide variability in these studies and so no firm conclusions can be drawn from this review. For example, the repeated dose studies range from investigations of two doses in a single day to multiple doses over several weeks. An additional limitation, as noted earlier, is the fact that far fewer studies (and test findings) are available in this review for the effects of repeated dosing. *Therefore, no figure is included here for the limited number of repeated dose findings and the remainder of the results section will focus only on the acute dose findings.*

3.2. Impairment by Individual Drugs as a function of Acute Dose Level

As noted earlier, details of the impairment findings as a function of drug generation, individual drugs, as well as specific dose can be found in Appendix B (e.g., number of NO versus YES impairment findings as well as %YES; presented for each category as well as for summaries).

3.2.1 Dose Response Curves for Objective Measures (Figure 3A)

Looking at the overall findings for all objective measures grouped together, the acute dose findings for each drug separately show the clearest dose response effects for all of the 1st generation drugs except perhaps chlorpheniramine. And, while the 2nd generation drugs typically show few findings of any significant impairment, a dose-response still is apparent. That is, when impairment was reported, usually a higher dose was being tested.

3.2.2 Objective Measures by Individual Drugs and by Generation (Figure 3B)

For the 2nd-generation drugs, all 45 findings for astemizole, with doses ranging from 10 to 40 mg, showed no significant impairment. In contrast, cetirizine was reported to cause significant impairment of objective measures in 18% of the cases (14 of 80 findings), whereas the other 2nd generation drugs had fewer reports of impairment (4 of 53 findings or 8% for loratadine, and 5 of 126 findings or 4% for terfenadine). As expected, the 1st generation drugs more often showed significant impairment: 61% (70 of 114 findings) for tripolidine and 53% (112 of 211 findings) for diphenhydramine, the two drugs used most frequently as positive control treatments in many of the studies.

3.2.3 Dose Response Curves for Subjective Measures (Figure 4A, Table 4 in Appendix A)

The subjective measures reveal even stronger dose response curves, particularly for the typically sedating 1st generation drugs. For example, significant sedation was reported increasingly more often when higher doses of diphenhydramine were tested: 57% for 25 mg, 71% for 50 mg, 85% for 75 or 100 mg, and 100% for >100mg. In contrast, the 2nd generation drugs were strikingly devoid of any significant findings of subjective sedation, that is, with the exception of cetirizine. Specifically, at all doses tested, cetirizine was reported to show some evidence of significant sedation: 33% (1 of 3 findings) for 5 mg, 14% (2 of 14 findings) for the indicated dose of 10 mg, and 17% (1 of 6 findings) for the highest dose tested, 20 mg.

3.2.4 Subjective Measures of Sedation by Individual Drugs and by Generation (Figure 4B)

Looking at the subjective measures of sedation by drug generation, the older H₁-antagonists had significant findings for 67% of the cases (62 of 92 findings) in contrast to only 5% (4 of 79 findings) for the newer drugs. As noted, cetirizine was the only 2^{nd} -generation drug showing significant sedation (17%, 4 of 23 of the findings), whereas each of the five 1^{st} -generation drugs produced significant sedation in over 50% of the times tested. Specifically, significant impairment was reported in 55% (6 of 11) of the test findings for clemastine, 64% (18 of 28 findings) for tripolidine, 67% (8 of 12 findings) for chlorpheniramine, 72% (26 of 36 findings) for diphenhydramine, and 80% (4 of 5 findings) for hydroxyzine.

3.3. Acute Dose Impairment by Behavioral Categories

This next section presents the impairment results of the reviewed studies as a function of the 10 behavioral categories of driving-related performance measures. As noted earlier, only the acute dose findings are presented since there were relatively few repeated dose studies.

3.3.1. **DRIVING AND PILOTING** (Figure 5, Table 5 in Appendix A)

There were 55 testing findings produced by the 17 studies which examined the effects of at least one of the key drugs on driving behaviors. Note that this category includes measures of actual driving on the road, or in a closed course, as well as a variety of measures from many different types of driving simulators and some piloting tasks. With such a wide range of different tasks and measures, it is not surprising that some of the tasks are not sensitive and so, for the 1st generation drugs as a class, only 48% (11 of 23) of the findings showed significant impairment. This compares to significant impairment reported in 13% (4 of 32) of the findings for the 2nd generation drugs.

Notably, when considering only the specific subset of *on-road driving* measures, the number of significant findings of impairment by the 1st generation drugs is much more pronounced, with 89% (8 of 9 findings) showing significant on-road driving impairment, versus only 10% (2 of 20 findings) for the 2nd generation drugs. Also, looking at the findings for the individual drugs, it is clear that all of the 1st generation drugs studied consistently show the on-road driving impairment. In contrast, the only 2nd generation drugs showing significant impairment of on-road driving skills were cetirizine (1 of 2 findings) and terfenadine (1 of 11 findings). The findings for these two drugs mirror those for the complete group of driving measures. That is, significant impairment of any type of driving-related behavior was found in 29% (2 of 7 tests) of the findings for cetirizine and in 13% (2 of 16 test findings) for terfenadine. The other two 2nd generation drugs studied showed no impairment; (astemizole was not studied).

3.3.2. **PSYCHOMOTOR SKILLS** (Figure 6, Table 6 in Appendix A)

A total of 35 studies evaluated the impairing effects of antihistamines on psychomotor skills and yielded 70 test findings. For the 1st generation drugs, 44% (22 of 50) of the findings showed significant impairment whereas none of the 20 findings for the 2nd generation drugs demonstrated significant impairment. (However, only astemizole, cetirizine and terfenadine were studied). Again, there is considerable variability in the type of psychomotor skills and specific task demands evaluated in these studies. Thus, this behavioral category does not appear particularly sensitive to detecting impairment. Of note, analysis of the specific subcategories revealed that tasks measuring balance (e.g., body sway, hand steadiness) seemed most sensitive to impairment by the 1st generation drugs (10 of 15 findings, or 67% versus none of the 4 tests for the 2nd generation drugs). In contrast, tasks requiring dexterity (e.g., picking up beads and other fine-motor tasks) were notably insensitive: none of the findings (4 each) for either the 1st generation or the 2nd generation drugs showed significant performance deficits. In addition, finger tapping tests were found to show significant impairment for 50% (8 of 16) of the findings for 1st generation drugs versus none of the 3 tests for the 2nd generation drugs.

3.3.3. **PERCEPTION**(Figure 7, Table 7 in Appendix A)

This category reflects varied tasks of perception (e.g., visual discrimination, time estimation) including singular visual search tasks (i.e., those *not* performed in the context of divided attention). No clear conclusions can be made for this category, however, since the available data from this review are quite limited: 14 studies produced a total of 26 test findings. For the 1st generation drugs, 35% (6 of 17) of the findings for the 1st generation drugs evidenced significant impairment of perceptual tasks whereas no impairment was reported in any of the 9 tests for the 2nd generation drugs (which only included astemizole, cetirizine and terfenadine). Looking at the figures for the individual 1st generation drugs, however, it appears that diphenhydramine was more often impairing than not (56% or 5 of 9 test findings) for perceptual tasks.

3.3.4. VISUAL FUNCTIONS & CRITICAL FLICKER FUSION (Figures 8A & 8B, Table 8)

Measures of visual functions included saccadic eye movements, smooth pursuit, dynamic visual acuity, visual field, pupillary diameter and extraocular muscle control. Such measures were examined in 16 studies, producing 31 test findings regarding impairment. Significant impairment was found in 10 of the 15 tests (67%) for the 1st generation drugs versus only 1 of the 16 tests (6%) for the 2nd generation drugs. It should be pointed out, however, that the single finding of significant impairment for the 2nd generation drugs involved dynamic visual acuity and loratadine 40 mg, a dose which is much higher than the recommended 10 mg dose. It also should be noted that the most often studied 1st generation drug for this visual function category was tripolidine 10 mg which was found to cause significant impairment in 89% (8 of 9) of the tests. Since all of these test findings came from the same group of investigators, however, one cannot tease apart the effect of tripolidine versus the inherent greater sensitivity (i.e., via decreased variability) afforded by using a single, standardized measure, namely dynamic visual acuity, and by the same group of investigators.

Some investigators have classified critical flicker fusion (CFF) as a measure of information processing while others consider it to reflect a more basic visual perception task. In this review, the CFF task simply was analyzed separately as a subset of the visual functions category. A total of 29 studies examined CFF, producing 52 test findings. Significantly impaired CFF was found in 52% (15 of 29) of the test finding for the 1st generation drugs. In contrast, the 2nd generation drugs were only found to impair CFF in one of the 23 times tested (4%); this single finding involved terfenadine 60 mg. As was the case with visual functions, the significant impairment by 1st generation drugs was most apparent in the studies of tripolidine (100% of the 10 tests). Again, the consistency of these findings may be due partly to the fact that they largely came from the same investigators who were using a more homogenous set of standardized CFF measures and methods.

3.3.5. COGNITIVE TASKS (Figure 9, Table 9 in Appendix A)

The category of cognitive tasks includes tasks of complex psychomotor skills (e.g., card sorting), memory (auditory and visual), trail-making tests and a variety of tasks requiring problem solving (arithmetic, numerical and logical reasoning) and cognitive flexibility (Stroop color/word task). As such, this category of cognitive tasks, like psychomotor skills, reflects a wide range of tasks and measures with the result of increased variability and concomitant decreased sensitivity to detecting impairment. Of the 63 studies which examined cognitive tasks, a total of 201 test findings evaluated impairment. For the 1st generation drugs, only 37% (46 of 126) of the test findings showed statistically significant impairment as compared to only 3% (2 of 75 tests) for the 2nd generation drugs. Moreover, the two cases of impairment for the 2nd generation drugs involved higher than recommended doses, cetirizine 20 mg and loratadine 40 mg, and both tested digit symbol substitution skills.

Given the large number of test findings and the wide variety of tasks represented, specific subsets of cognitive tasks also were analyzed. Results showed that digit symbol substitution tests were found to be impaired by 1st generation drugs in 38% (17 of 45) of the test findings versus only 7% (2 of 28 findings) for the 2nd generation drugs. Memory tasks were impaired in 39% (13 of 33) of the tests of 1st generation drugs whereas no significant memory impairment was found in any of the 13 tests for the 2nd generation drugs. Trail-making tasks appeared to provide the most sensitive measures in this category, albeit with rather limited data available in this review, with 50% (5 of 10) of the findings for the 1st generation drugs.

3.3.6. **DIVIDED ATTENTION** (Figure 10, Table 10 in Appendix A)

Divided attention tasks were examined in 28 studies, producing 52 test findings concerning impairment. Typically, the divided-attention task consisted of the concurrent performance of a tracking and visual search task. In other cases, some investigators employed other types of dual tasks such as simultaneous tracking and continuous memory tasks. As expected, given the complex demands of most divided-attention tasks, this behavioral category was found to be relatively sensitive for detecting significant impairment. The 1st generation drugs were found to impair divided-attention skills in 69% (20 of 29) of the findings versus 13% (3 of 23 test findings) for the 2nd generation drugs. The most frequently studied 1st generation drug, diphenhydramine, was found to impair divided-attention tasks in 77% (13 of 17) of test findings. For the 2nd generation drugs, one finding of significant impairment was found for each of the following drugs: cetirizine (from a total of 6 tests), loratadine (of 8 tests) and terfenadine (of 8 tests); all of these significant findings occurred at the recommended doses. Interestingly, two cases of an apparent performance-enhancing effect (i.e., performance was significantly better after the active drug relative to placebo) also were reported for loratadine 10 mg (Kay et al., 1997) and terfenadine 60 mg (Moskowitz & Burns, 1988). This suggests there may be a possible arousing or stimulating effect of these specific 2nd-generation drugs.

3.3.7. VIGILANCE TASKS (Figure 11, Table 11 in Appendix A)

Vigilance was evaluated in 25 studies, producing a total of 46 test findings. As clearly shown in the figures, both for each drug as well as for the overall findings by drug generation, nearly all of the 1st generation drugs consistently were found to cause significant impairment of the measures of sustained attention. In marked contrast, not one of the 2nd generation drugs showed any evidence of impairment. By generation, the older drugs were found to impair vigilance 86% of the times tested (25 of 29 findings) whereas all 17 tests for the new drugs found no evidence of any significant impairment. Such findings attest to the sensitivity of vigilance tasks to detect CNS sedation.

Moreover, an interesting finding concerning vigilance comes from an earlier study in our laboratory (Moskowitz & Burns, 1988). In brief, that study found an apparent alerting or stimulating effect evidenced in the terfenadine 60 mg treatment condition which showed *better* vigilance performance (i.e., faster response times) relative to the placebo control. As noted earlier, fexofenadine has a chemical structure nearly identical to that of terfenadine's active metabolite. The single study of fexofenadine (Vermeeren & O'Hanlon, 1998; Ref#122) also examined vigilance but found neither impairment nor improved performance. The authors of that study suggested that such findings indicate that fexofenadine does not act pharmacologically like classic stimulants since typically the "latter enhance signal detection performance in vigilance tests." Of note, as discussed for some of the other behavioral categories, there are a number of findings in this review of other apparently alerting or stimulating effects reported for terfenadine. Since the safety implications of this issue need to be evaluated in more depth, additional studies of the 2nd-generation drugs are eagerly awaited. This is particularly important for fexofenadine, since it is only beginning to be studied and terfenadine is no longer on the market.

3.3.8. TRACKING (Figures 12A & 12B, Table 12 in Appendix A)

A total of 80 test findings was produced by the 39 studies which evaluated tracking performance. This behavioral category included measures of different types of tracking tasks, including pursuit, compensatory, critical and adaptive tracking. Significant impairment was reported for 69% (33 of 48 tests) versus 19% (6 of 32 tests), respectively, of the findings for the 1st and 2nd generation drugs. As seen in Figure 12A, for the individual drugs, all five of the 1st generation drugs demonstrated significant impairment for nearly all test findings reviewed. In contrast, for the five 2nd-generation drugs tested, only cetirizine and fexofenadine were found to impair tracking. Specifically, two of the three findings for cetirizine, and both of the two findings for fexofenadine, showed significantly impaired tracking performance.

Focusing next on the subset of 26 studies which evaluated *either critical or adaptive tracking* (Figure 12B), the 52 test findings for this specific subcategory revealed significant impairment for over 90% (28 of 31) of the findings for the 1st generation drugs, in contrast to 19% (4 of 21 findings) for the 2nd generation drugs. Moreover, two of the three findings of no impairment for the older drugs actually showed trends (p < 0.08). Therefore, if a less stringent criterion for statistical significance is allowed, the findings of impairment by the 1st generation drugs increase to 97% (30 of 31 findings). Clearly, consistent with what prior investigators and reviewers have reported, the current review's findings confirm that critical and adaptive tracking tasks appear to provide sensitive measures of driving-related performance.

3.3.9. **REACTION TIME** (Figure 13, Table 13 in Appendix A)

This category included simple and complex reaction time tasks, as well as some that were not easily classified into either category since the published task descriptions often were quite limited if not lacking. Overall, there were 50 studies which included reaction time tasks, producing 98 test findings for this behavioral category. For the 1st generation drugs, 48% (29 of 61) of the test findings were found to show significant slowing of reaction time; this compares to 11% (4 of 37 findings) for the 2nd generation drugs. As seen in Figure 13 for the individual drugs, diphenhydramine and tripolidine, respectively, had the most notable impairing effects (54% or 13 of 24 findings, and 50% or 6 of 12 findings), whereas cetirizine was the only 2nd generation drug showing significant impairment (40%, 4 of 10 findings).

Looking at the subcategories, the simple reaction time tasks appeared to be somewhat more sensitive to detecting impairment than were the complex (or choice) reaction time tasks, at least for the 1st generation drugs. Specifically, 42% (11 of 26) of the findings showed significant slowing of choice reaction time versus 60% (15 of 25 test findings) for simple reaction time. Perhaps the relative insensitivity of complex (or choice) reaction time tasks is due to the greater variation in the specific measures employed across studies. In contrast, there may be less variability in the measures of simple reaction time. However, for the 2nd generation drugs, no distinction was seen for the findings of significant slowing of simple reaction time (11% or 1 of 9 findings) versus complex reaction time (12% or 3 of 26 findings).

3.3.10. PHYSIOLOGICAL MEASURES OF SEDATION (Figures 14A & 14B, Table 14)

Physiological measures of sedation included spectral analysis of electroencephalograph (EEG) waves, evoked response potentials (ERP's such as P300, etc.), as well as the highly standardized Multiple Sleep Latency Test (MSLT) which utilizes EEG frequencies to detect the onset of sleep. A total of 23 studies evaluated one or more of these various objective measures

of sedation, producing 56 test findings. Significant objective sedation was reported for 79% (22 of 28) of the findings for the 1st generation drugs versus 14% (4 of 28 findings) for the 2nd generation drugs. As clearly evident in Figure 14A, all five of the older drugs showed significant sedation in most cases and three of the four new drugs also showed some sedation (there were no data for this category from the single fexofenadine study).

If we next focus only on the subset of the MSLT measures, as shown in Figure 14B, the results are quite striking. Now 100% of the 9 test findings for the 1st generation drugs shows significant sedation as compared to only 9% (1 of 11) of the findings for the 2nd generation. While admittedly small numbers of test findings are available, it is interesting that the single finding of significant objective sedation found for the new drugs is due to cetirizine which, consistent with the findings from many of the other behavioral categories in this review, seems to stand out in the group of otherwise *relatively* "non-sedating" new drugs.

4. SUMMARY AND DISCUSSION

4.1. Impairment as a function of Behavioral Tasks (Figure 15)

An overall summary of the acute dose impairment results, as a function of H1-antagonist generation and behavioral category (or subjective sedation), is presented in Figure 15. As clearly shown, the most sensitive objective measures for detecting sedation and impairment appear to be: the Multiple Sleep Latency Test, critical or adaptive tracking, vigilance, divided attention and some driving measures. On the other hand, the categories of cognitive tasks, perception and psychomotor skills all seem to lack sensitivity overall. This may be due, at least partly, to the greater variability across types of the tasks and measures employed in the studies reviewed. Finally, the subjective measures of sedation appear to be relatively sensitive, at least for the 1st-generation drugs.

Also apparent in Figure 15, and as expected, the 1st-generation drugs generally were found to impair and sedate substantially more often than did the 2nd-generation drugs. However, it is important to emphasize that some findings of statistically significant impairment also were reported for the 2nd-generation drugs, specifically for subjective sedation as well as for all of the behavioral categories except psychomotor skills, perceptual tasks, and vigilance. The greater heterogenity of measures employed across studies for these tasks may partially explain the lack of any significant findings at least for the first two categories. In contrast, however, despite the use of a considerably more homogenous group of vigilance measures across studies, the overall results still showed no significant impairment of vigilance by the 2nd-generation drugs. This is an important finding, given that histaminergic pathways are widespread in the CNS and appear to be related to mechanisms that support alertness and vigilance during the wakeful state (Nicholson et al. 1985). Thus, the newer, 2nd-generation histamine-antagonist drugs which claim to be "non-sedating" actually may reflect a true pharmacological advance at least in terms of eliminating any disruption of vigilance.

On the other hand, the repeated reports of apparent arousal or stimulating effects noted with terfenadine and some of the other 2nd-generation drugs suggest that additional study is needed. Although the newer H1-antagonists appear to be relatively devoid of impairing effects, the findings of faster response times and apparent performance enhancement clearly warrant closer scrutiny. What are the specific pharmacodynamic actions for such effects? And what, if any, are the driving safety implications? Only carefully designed studies, using sensitive and validated measures, can address this issue by examining if such increased arousal is associated, or not, with any concomitant disruption of the ability to continue to focus on the primary driving task. Or, is such increased arousal indicative of influences on physiological systems that are not primarily CNS?

4.2. Comparison with Impairment Findings for Alcohol

As noted earlier, alcohol's effects often are used as a benchmark for evaluating the degree of impairment by medicinal drugs. Therefore, a comparison of the results of this review with those from the first author's recent review of the effects of low to moderate BAC's on driving (Moskowitz & Fiorentino, 2000) is in order. Although neither of the current reviews specifically examined the magnitude of impairment associated with alcohol or the H1-antagonists, the

relative sensitivity of the various behavioral categories was summarized in each review. In brief, there are several areas of consistency, as well as discrepancy, across the findings from these two reviews. First, both reviews found support for the sensitivity of the following behavioral categories for detecting driving-related performance impairment: Multiple Sleep Latency Test (i.e., measure of wakefulness or arousal), tracking, vigilance and divided attention. Second, critical flicker fusion and simple reaction time were found to be insensitive measures for detecting alcohol's impairing effects, at least for low to moderate doses. In contrast, these two measures did appear to be relatively sensitive to the impairing effects of the 1st-generation antagonists. This suggests that different behavioral mechanisms may be involved. Thus, experimental studies of the effects of a given drug class must include specific measures related to that drug's actions, and not simply rely on the standard test batteries employed for assessing alcohol's effects.

Finally, in addition to examining impairment as a function of the behavioral tasks, as described above, there also are a number of issues which were not addressed in the current review since relevant studies were limited in availability. These issues are summarized briefly below:

4.3. Repeated Dosing And Tolerance Effects

There was a rather limited number of studies in this review which examined repeated doses. Moreover, they ranged from studies of two doses in one day to three or four doses per day over the course of two weeks. Thus, the wide variability of dosing schedules, as well as the limited number of repeated dose studies available for review, do not permit a systematic evaluation of the effects of repeated doses. Nonetheless, this is a very important issue since most individuals needing a medication do not simply take a single dose of a drug. Partial tolerance to sedation and impairment have been reported after repeated doses of the 1st-generation antihistamines in some studies (e.g., Bye et al., 1977; Walsh et al., 1994) but not in others (e.g., Alford et al., 1989; Brookhuis et al., 1993; Goetz et al., 1989). And evidence both for impairment (e.g., Volkerts et al., 1992) as well as for improved performance (e.g., Vermeeren & O'Hanlon, 1998) have been reported after chronic daily dosing with some of the 2nd-generation antihistamines, apparently due to drug accumulation. In the future, more studies will need to examine more systematically the effects of repeated doses of antihistamines.

4.4. Timing of Acute Doses Tested

Most studies tested for impairment or sedation within the window of expected peak drug effects, typically at two to three hours post-dose. Some studies utilized repeated test batteries over a five to eight hour period. However, in certain cases the lack of significant findings appeared due to testing either too early, or too late, to capture the peak drug effects. For example, two of the significant findings of impairment by cetirizine only occurred on specific measures and at much later times in the testing session, namely between 6 and 8 hours post-dose (Gengo et al., 1990; Walsh et al., 1992). Such effects clearly would be missed if the testing had only included a more limited number of measures or only earlier post-dose times as many of the other studies had done. Thus, future studies must assess the effects of antihistamines at the optimal post-dose times and employ a comprehensive, standardized test battery of the most sensitive and valid measures of sedation and driving-related impairment.

4.5. Specific Populations Tested

The typical subject population used in the majority of the studies reviewed was healthy volunteers, usually young to middle-aged men. Such a sample is appropriate as an initial step in a research program. However, more systematic research studies are needed to explore further the effects of antihistamines on other populations, including women, the elderly, and symptomatic versus asymptomatic allergy patients. In the latter case, studies are needed to evaluate whether the underlying allergy symptoms might actually contribute to impaired performance and, if so, if an antihistamine might improve performance (cf. Burns et al., 1994).

The effect of gender also may influence the test findings in terms of an inherent confound, namely women being relatively more susceptible to a given drug dose, due to their smaller body size. Indeed, of the very few significant findings of impairment by terfenadine, one was reported in a study which only tested women, and found that only the highest dose, 240 mg, caused driving-related impairment (e.g., Bhatti & Hindmarch, 1989).

Driving is a complex task requiring the integration of visual, psychomotor and cognitive skills. Age, and the various medical conditions and medications that often accompany aging, may compromise many of the skills needed to operate a motor vehicle safely. Elderly drivers are known to have a greater crash fatality risk (i.e., more fatalities when in a crash). A recent study of 3,238 drivers aged 65 and older specifically found that cognitive test performance remained significantly associated with crash risk even after controlling for driver age, race and measures of driving exposure (Stutts et al., 1998). Such findings support the validity of the various drivingrelated cognitive measures employed in the studies reviewed. However, there were relatively few studies which examined the effects of antihistamines on older subjects. Clearly, this area demands further study.

4.6. Clinical Efficacy Versus Side Effect Profile

Finally, another issue needing further study concerns the design of comprehensive and wellcontrolled studies which compare several antihistamines, with each drug tested at its indicated therapeutic dose, for clinical efficacy (i.e., using wheal and flare tests, the standard skin reaction measures of peripheral allergic effects), subjective sedation, and behavioral toxicity, all within the same study. In the current review, there is only one example of the use of such an exemplary design. It is the study by Simons et al. (1996; Ref#114) which evaluated the effects of five 2nd-generation H1-antagonists (astemizole, cetirizine, loratadine, terfenadine, ketotifen) in comparison to placebo and to the 1st-generation drug, diphenhydramine, as the positive control. The results showed that:

1) compared to placebo, the 1st-generation drug caused both significant subjective sedation and objective impairment;

2) the 2nd-generation drugs were *relatively* devoid of significant sedation or impairment, with the exception of cetirizine which caused significant sedation; and

3) even the 2nd-generation drugs showed some evidence of sedation or impairment relative to placebo, although the magnitude of the effects generally were not statistically significant.

It should be noted that the Simons et al. (1996) study is limited by its use of only a single objective measure of impairment, namely the evoked response potential. The results of that single study are notable, however, in that they closely mirror the findings of this current review of the findings across many studies. Thus, despite the limitations noted of the studies in this review, the overall findings do appear to be representative of the effects of the antihistamines.

5. CONCLUSIONS

- 5.1. There is some slight, but ambiguous, evidence from epidemiological studies of a connection between antihistamine use and traffic collision rates. Of note, these epidemiological studies were done primarily when the use of 1st-generation (but not 2nd-generation) antihistamines was prevalent.
- 5.2 There is overwhelming evidence from the experimental literature that the 1st-generation antihistamines produce objective signs of skills performance impairment as well as subjective symptoms of sedation.
- 5.3 The 2nd-generation antihistamines show low incidence of objective skills performance impairment and in the majority of cases no evidence of subjective sedation.
- 5.4 While 2nd-generation antihistamines represent a major triumph for the pharmaceutical industry in reducing potential side effects, there still remains some evidence that all antihistamines, even the 2nd- generation drugs, can have objective skills impairment consequences at least in some cases.
- 5.5 Within both the 1st- and 2nd-generation antihistamine groupings, there is considerable variation in objective evidence of impairment. Additionally, for the 1st-generation antihistamines, there is considerable variation in subjective effects, such as sedation. Within each generation of antihistamines, there clearly are drugs that are to be preferred for use to avoid side effects.
- 5.6. It would appear that proper selection of a 2nd-generation antihistamine would produce little skills performance impairment and only a small effect on traffic collisions.
- 5.7. Methodologically, it is apparent that among the many diverse techniques for investigating driving-related impairment, some methods and behavioral domains are more sensitive to the effects of antihistamines. Obviously, reports of the rate of impairment can be manipulated by a failure to use sensitive measures or test at appropriate post-dose times. In future studies of antihistamines, therefore, it would be hoped that more utilization will be made of the most methodologically-sound techniques so as to permit a better comparison between different drugs.

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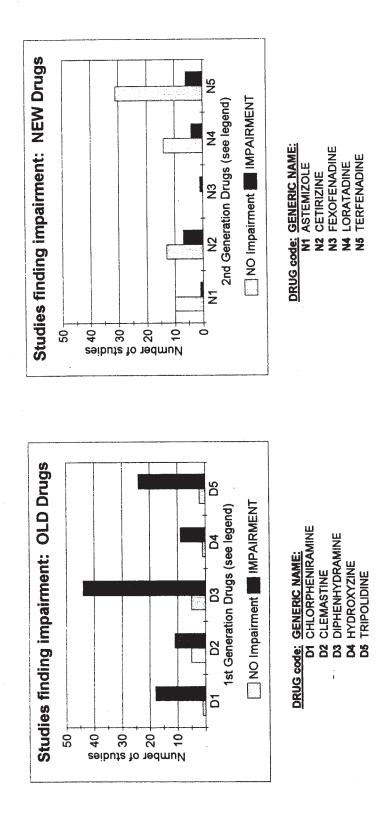
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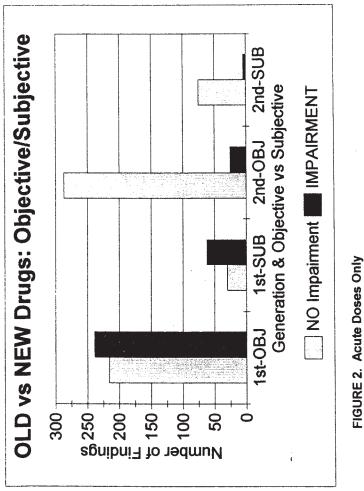
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FIGURES

(Appearing as a complete set, from #1 through #15)







Results shown for: TASK CATEGORY: OBJECTIVE MEASURES SC#: 1-10

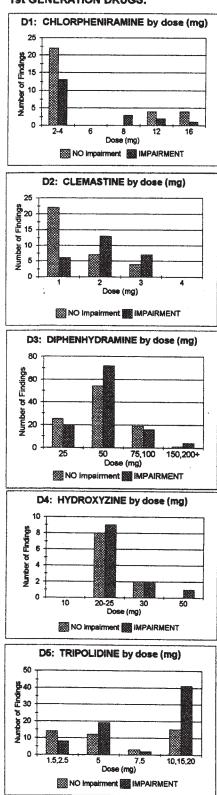
DOSING:

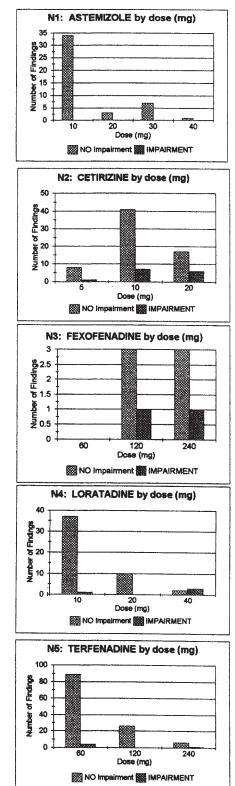
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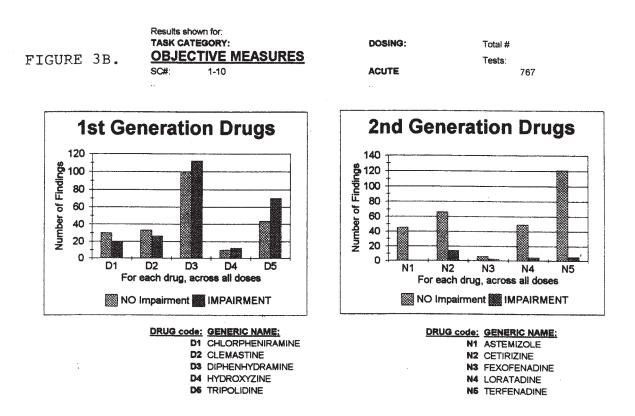
1st GENERATION DRUGS:

FIGURE 3A.

2nd GENERATION DRUGS:







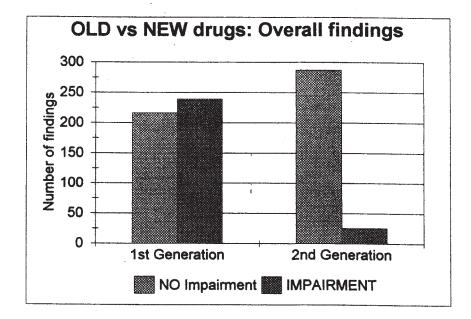


FIGURE 4A.

Results shown for: TASK CATEGORY: SUBJECTIVE SEDATION SC#: 99

DOSING:

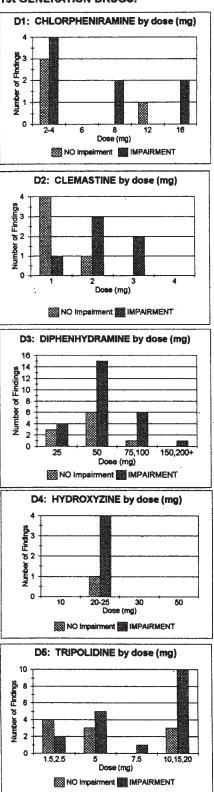
Total # Tests: 171

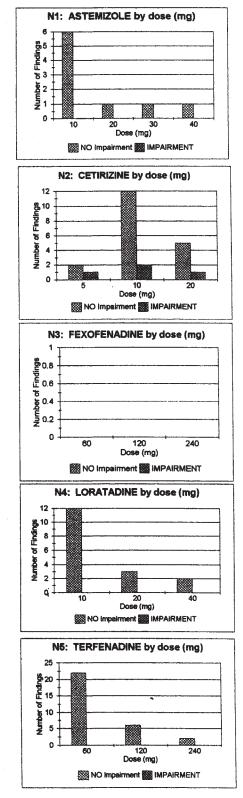
ANTIHISTAMINES: H1-RECEPTOR ANTAGONISTS by DRUG GENERATION:

1st GENERATION DRUGS:

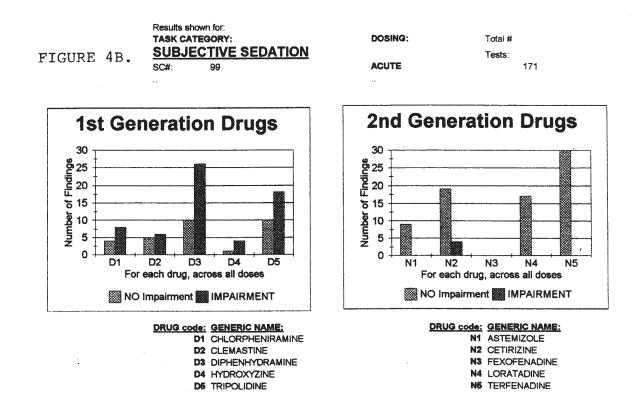


ACUTE

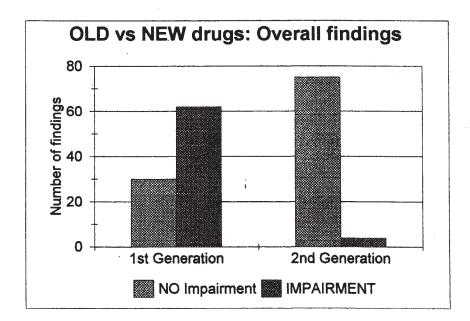


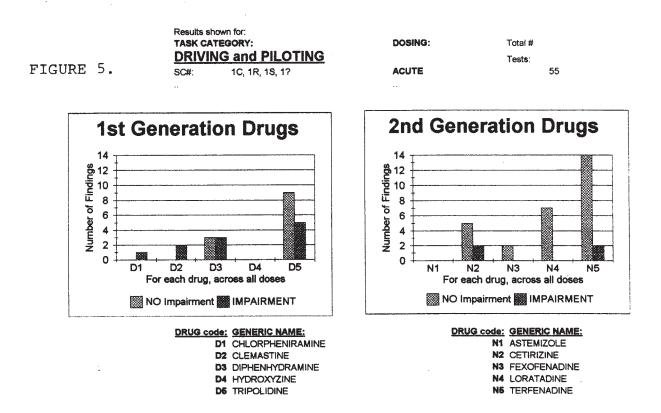


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SUBJECTIVE SEDATION





DRIVING and PILOTING

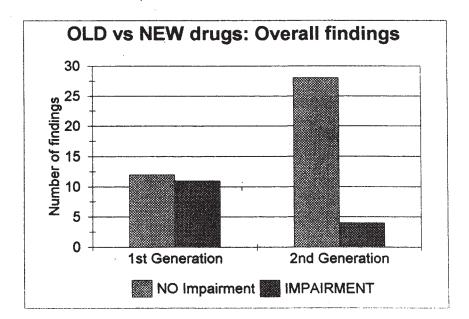
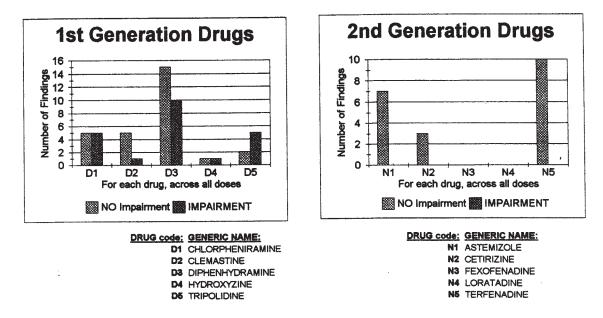


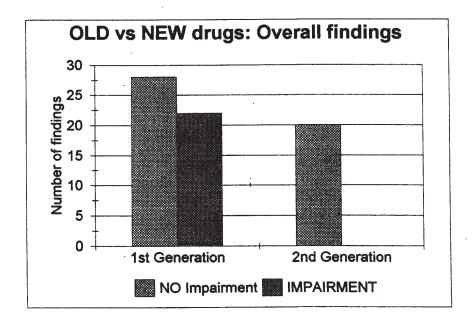
FIGURE 6.

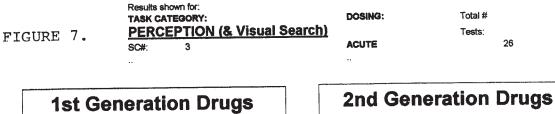
Results shown for: TASK CATEGORY: PSYCHOMOTOR TASKS SC#: 2 (2,28,2D,2T)

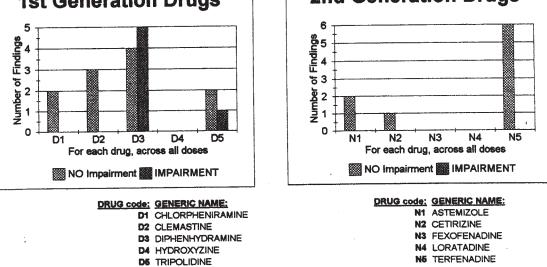
DOSING:	Total #
	Tests:
ACUTE	70



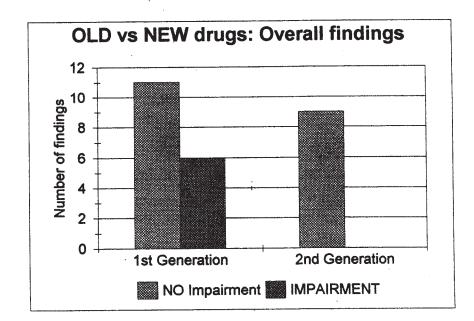


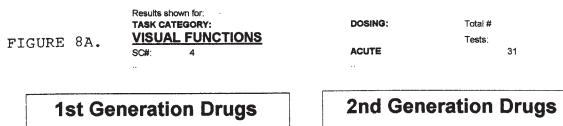


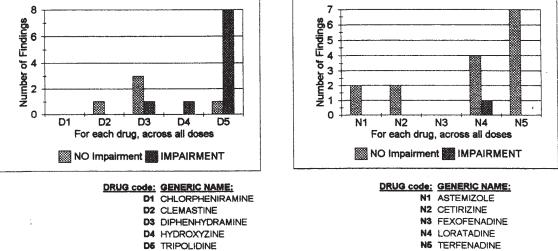




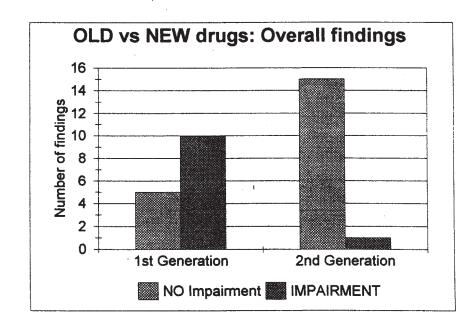
PERCEPTION (& Visual Search)

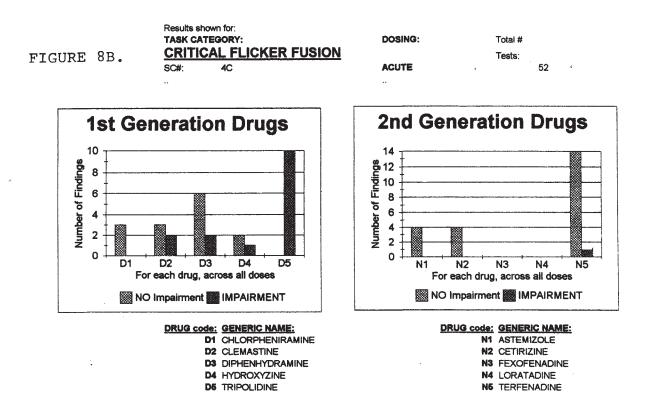






VISUAL FUNCTIONS







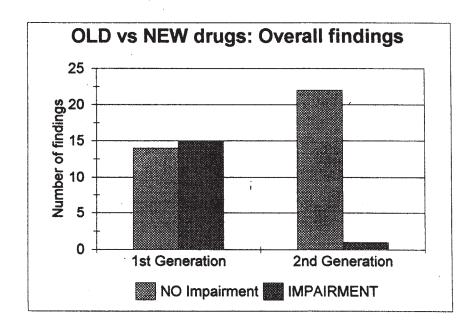
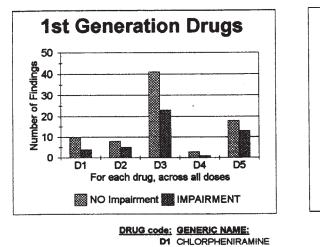


FIGURE 9.

Results shown for: TASK CATEGORY: COGNITIVE TASKS SC#: 5 (5D,5M,5T)

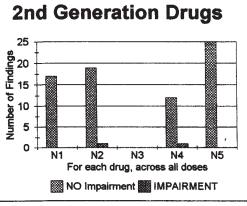
DOSING:	Total #
ACUTE	Tests: 201



D2 CLEMASTINE

D4 HYDROXYZINE D5 TRIPOLIDINE

D3 DIPHENHYDRAMINE



DRUG code: GENERIC NAME: N1 ASTEMIZOLE N2 CETIRIZINE N3 FEXOFENADINE N4 LORATADINE

N5 TERFENADINE

COGNITIVE TASKS

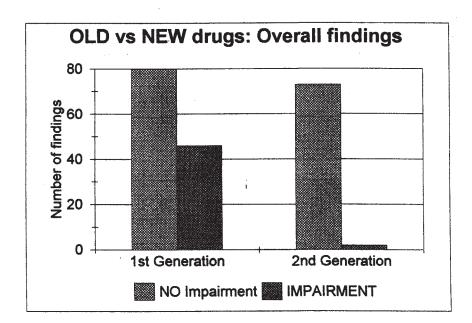
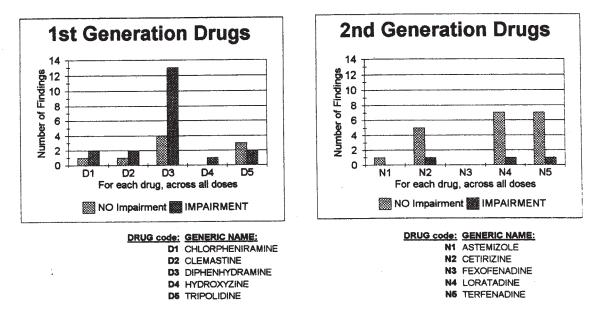


FIGURE 10.

Results shown for: TASK CATEGORY: DIVIDED ATTENTION SC#: 6

DOSING:	Total #
	Tests:
ACUTE	52



DIVIDED ATTENTION

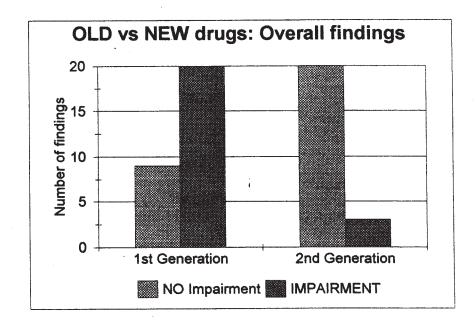
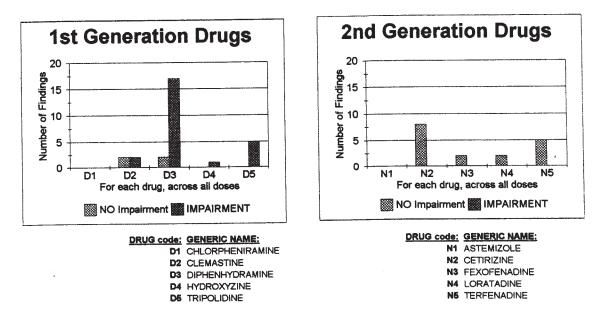


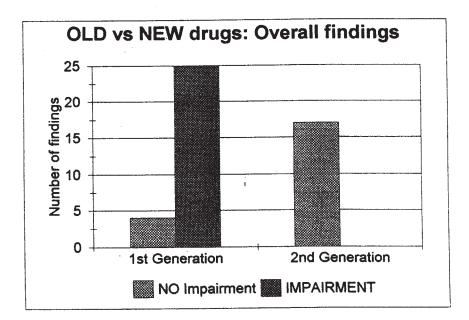
FIGURE 11.

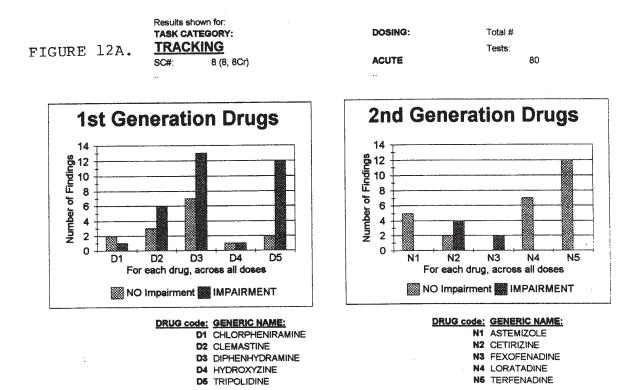
Results shown for: TASK CATEGORY: VIGILANCE	
SC#: 7 (7?)	

DOSING:	Total #	
	Tests:	
ACUTE		46

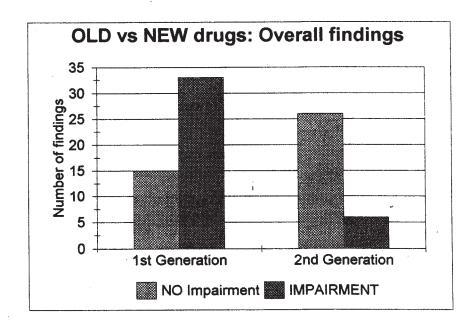


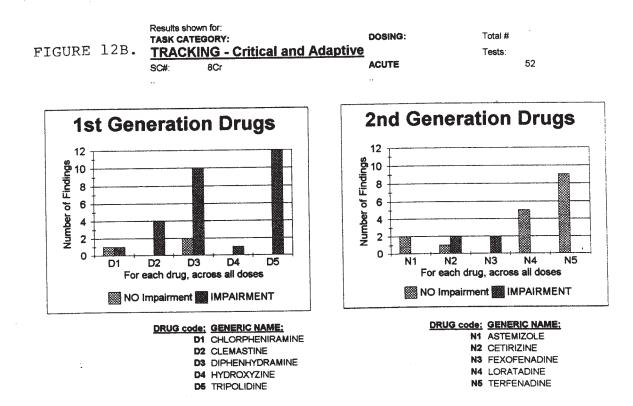
VIGILANCE



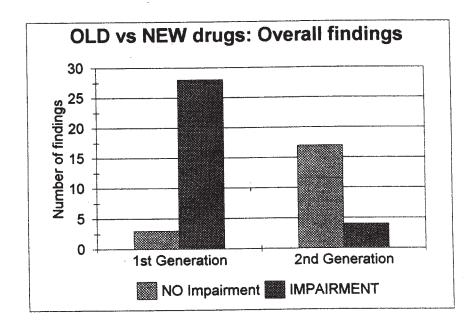


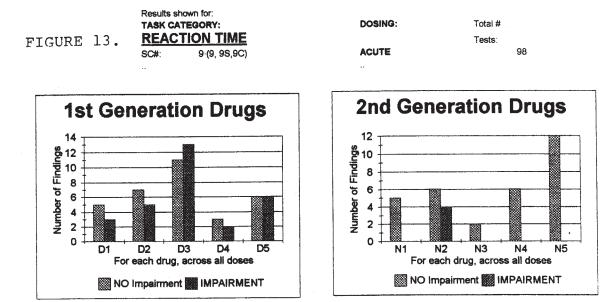
TRACKING

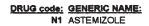












N2 CETIRIZINE N3 FEXOFENADINE

N4 LORATADINE

N5 TERFENADINE

REACTION TIME

DRUG code: GENERIC NAME:

D2 CLEMASTINE

D5 TRIPOLIDINE

D1 CHLORPHENIRAMINE

D3 DIPHENHYDRAMINE D4 HYDROXYZINE

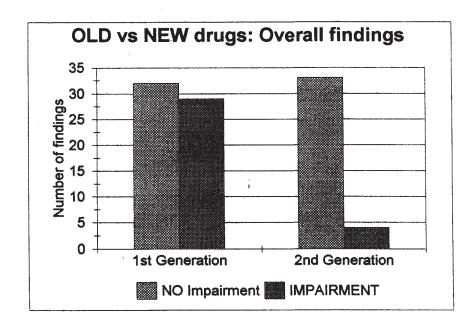
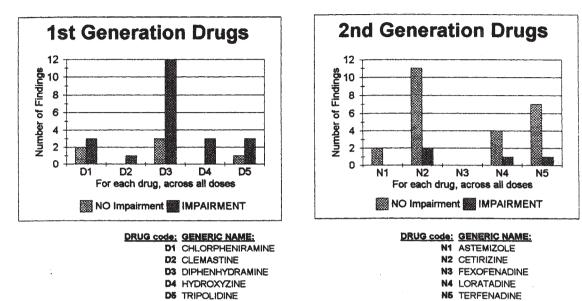


FIGURE 14A.

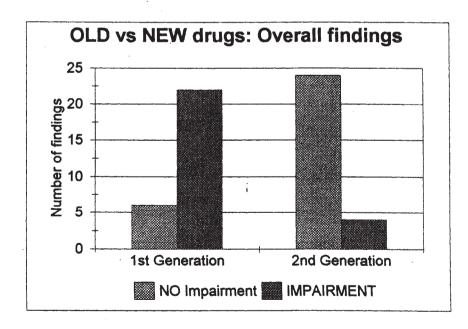
TASK CATEGORY: PHYSIOLOGICAL SEDATION SC#: 10 (10, 10M) EEG, ERP, MSLT

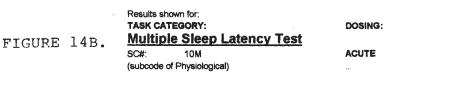
Results shown for:

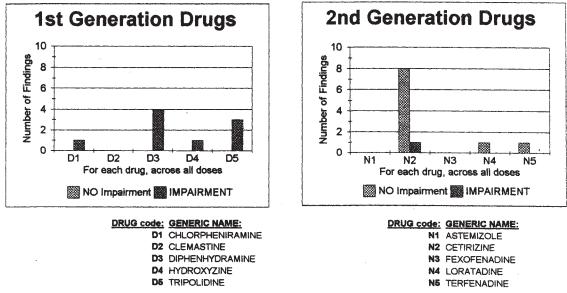
DOSING:	Total #
ACUTE	Tests: 56



PHYSIOLOGICAL SEDATION





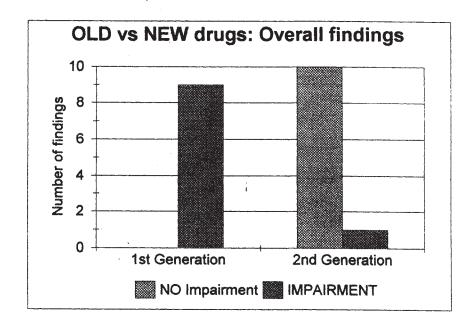


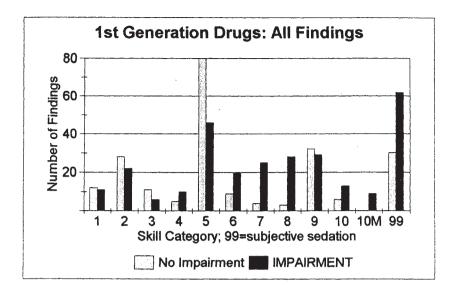
Total #

Tests:

20

Multiple Sleep Latency Test





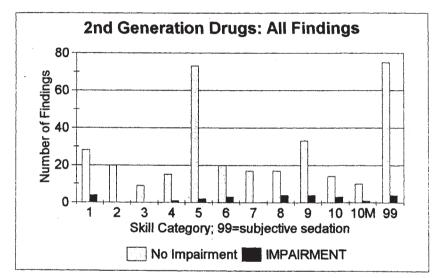


FIGURE 15. Overall Summary

SC#: SKILL CATEGORIES:

- 1 DRIVING & PILOTING
- 2 PSYCHOMOTOR
- 3 PERCEPTION
- 4 VISUAL FUNCTIONS, but not CFF
- 5 COGNITIVE TASKS
- 6 DIVIDED ATTENTION
- 7 VIGILANCE
- 8 TRACKING only critical & adaptive
- 9 REACTION TIME
- 10 PHYSIOLOGICAL EEG, ERP
- 10M Multiple Sleep Latency Test
- 99 SEDATION SUBJECTIVE

APPENDICES

Appendix A Tables of Impairment Findings by Behavioral Category (Listings by Study & Drug)

Appendix B EXAMPLE of an Impairment Summary Sheet (YES/NO Counts) by Behavioral Category

Appendix C EXAMPLE of a Study Summary Sheet (n=138 studies from 130 references)

Appendix D Summary Table of Impairment Findings by Study (includes all 10 Drugs) Appendix A

Tables of Impairment Findings by Behavioral Category

(Listings by Study & Drug)

SEDATION - SUBJECTIVE MEASURES - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only

TABLE 4.

Sheet: SEDATION

	Sheet: SEDATION Page 2: sorted by Generation, DF REFERENCE	RUG, Dose, Ref#, Measure MEASURE of Subjective Sedation	8. * *		DRUG	Dose ing	IMPAIR YES	
\$85			0		Generation Drugs:	. 00		
					•			
8	Biehl (1979)	SEDATION - VAS of mood adjectives	99	1	CHLORPHENIRAMINE	4		NO
26	Clarke & Nicholson (1978)	SEDATION - VAS	99	1	CHLORPHENIRAMINE	4	YES	NO
35	Dhorranintra et al. (1990)	SEDATION - VAS & Alertness rating	99 99	1	CHLORPHENIRAMINE	4	YES	1
61 76	Kulshrestha et al. (1978) Nicholson (1979)	SEDATION - VAS for Sedation SEDATION - VAS	99	1	CHLORPHENIRAMINE	4		NO
120	Unchern et al. (1986)	SEDATION - 7-pt ratings & Sx report	99	1	CHLORPHENIRAMINE	4	YES	
131B	Witek, Jr. et al. (1995)	SEDATION - VAS (PC), SSS	99	1	CHLORPHENIRAMINE	4	YES	
69	Meador et al. (1989)	SEDATION - reported occurrences	99	1	CHLORPHENIRAMINE	8	YES	
83	Nicholson et al. (1991)	SEDATION - VAS, Stanford (SSS)	99	1	CHLORPHENIRAMINE	10	YES	
63	Lee et al. (1988)	SEDATION - factor 1 of Mood ratings	99	1	CHLORPHENIRAMINE	12		NO 6P
25	Chapman & Rawlins (1982)	SEDATION - VAS	99	1	CHLORPHENIRAMINE	16	YES	
59	Khosla et al. (1993)	SEDATION - VAS	99	1	CHLORPHENIRAMINE	16	YES	
26	Clarke & Nicholson (1978)	SEDATION - VAS	99	1	CLEMASTINE	1		NO NO WP
42	Gaillard et al. (1988)	SEDATION - VAS scales	99 99	1	CLEMASTINE	1	1	NO
91	Peck et al. (1975)	SEDATION - VAS set of states	99	1	CLEMASTINE	1	1	NO
97 112	Reinberg et al. (1978) Seppaia et al. (1981)	SEDATION - (~VAS rectangle 22cm)	99	1	CLEMASTINE	1	YES	
53	Hopes et al. (1992)	SEDATION - Adjective checklists	99	1	CLEMASTINE	2	YES	
87	Patat et al. (1994)	SEDATION - VAS series (LARS)	99	1	CLEMASTINE	2		NO WP
91	Peck et al. (1975)	SEDATION - VAS set of states	99	1	CLEMASTINE	2	YES	
124	Vuurman et al. (1994)	SEDATION - VAS, Bond & Lader	99	1		2	YES	
64	Levander et al. (1985)	SEDATION - VAS; 3/6 sets = sedation	99	1		3	YES	
97	Reinberg et al. (1978)	SEDATION - (~VAS rectangle 22cm)	99	1		3 25	YES	NO
27	Cohen et al. (1984)	SEDATION - VAS; on drive day	99 99	1		25 25	YES	
27 30	Cohen et al. (1984) Curran et al. (1998)	SEDATION - VAS; on lab day SEDATION - VAS	99	1		25	1.00	NO
30	Fine et al. (1994)	SEDATION - POMS (PC)	99		# · · · · = · · · · · · · · ·	25	YES	
120	Unchem et al. (1986)	SEDATION - 7-pt ratings & Sx report	99	1		25	YES	
134	Scavone et al. (1998)	SEDATION - VAS lines	99	1	DIPHENHYDRAMINE	25		NO
131B	Witek, Jr. et al. (1995)	SEDATION - VAS (PC), SSS	99	1	DIPHENHYDRAMINE	25	YES	
4	Berlinger et al. (1982)	SEDATION - VAS sed, mood adjectives	99	1		50		NO
20	Burns et al. (1999 - ms)	SEDATION - VAS	99	1		50		NO
24	Carruthers et al. (1978)	SEDATION - VAS	99			50 50 -	YES	20
27	Cohen et al. (1984)	SEDATION - VAS; on drive day	99 99			50 ·	YES	NO
27 29	Cohen et al. (1984) Cohen et al. (1987)	SEDATION - VAS; on lab day SEDATION - VAS	99			50	YES	
30	Curran et al. (1998)	SEDATION - VAS	99	- 12	DIPHENHYDRAMINE	50	YES	
39	Fink et al. (1979)	SEDATION - Alertness rating	99	- 8	DIPHENHYDRAMINE	50	YES	
44	Gengo et al. (1990)	SEDATION - VAS, Stanford (SSS)	99		DIPHENHYDRAMINE	50	YES	
57	Kaye et al. (1997)	SEDATION - Stanford SSS, VAS, Moods	99	•	1 DIPHENHYDRAMINE	50	YES	
66	Lines et al. (1997)	SEDATION - VAS; Bond & Lader Factor 1	99	14	1 DIPHENHYDRAMINE	50		NO
110	Schweitzer et al. (1994)	SEDATION - VAS	99	- 10	1 DIPHENHYDRAMINE	50	YES	
114	Simons et al. (1996)	SEDATION - VAS based on SSS	99	14	1 DIPHENHYDRAMINE 1 DIPHENHYDRAMINE	50 50	YES	
116 119	Spector et al. (1980) Tharion et al. (1994)	SEDATION - VAS (mean of 8) SEDATION - POMS, Sx Q	99		1 DIPHENHYDRAMINE	50	1.53	NO
127	Wilkinson & Moskowitz (1990)	SEDATION - POMS	99	H	1 DIPHENHYDRAMINE	50	YES	
129	Wilkinson et al. (1999 - ms)	SEDATION - VAS	99	- 10	1 DIPHENHYDRAMINE	50		NO
130A	Witek, Jr. et al. (1992)	SEDATION - VAS (PC), SSS	99		1 DIPHENHYDRAMINE	50	YES	
130B		SEDATION - VAS (PC), SSS	99		1 DIPHENHYDRAMINE	50	YES	
131A		SEDATION - VAS (PC), SSS	99	- 0	1 DIPHENHYDRAMINE	50	YES	
131B		SEDATION - VAS (PC), SSS	99		1 DIPHENHYDRAMINE	50	YES	
27 27	Cohen et al. (1984) Cohen et al. (1984)	SEDATION - VAS; on drive day SEDATION - VAS; on lab day	99		1 DIPHENHYDRAMINE 1 DIPHENHYDRAMINE	100 100	YES	
68	Mattila et al. (1986)	SEDATION - VAS	99		1 DIPHENHYDRAMINE	100	YES	
70	Mohs et al. (1978)	SEDATION - reported occurrences	99	- 44	1 DIPHENHYDRAMINE	100	YES	
71	Moser et al. (1978)	SEDATION - 9-pt VAS: tired, dull	99		1 DIPHENHYDRAMINE	100	YES	
94	Preston et al. (1992)	SEDATION - DEQ: Alert-Sleepy scale	99		1 DIPHENHYDRAMINE	100		NO
106	Saarialho-Kere et al. (1989)	SEDATION - VAS set of states	99		1 DIPHENHYDRAMINE	100	YES	
94	Preston et al. (1992)	SEDATION - DEQ: Alert-Sleepy scale	99		1 DIPHENHYDRAMINE	200	YES	
64 65	Levander et al. (1985)	SEDATION - VAS; 3/6 sets = sedation	99	18		20	YES	
65 43	Levander et al. (1991) Gengo et al. (1987)	SEDATION - VAS; 3/7 sets = sedation	99			20 25	YES	
43	Seidel et al. (1987)	SEDATION - VAS SEDATION - VAS, Stanford (SSS), POMS	99	1	1 HYDROXYZINE 1 HYDROXYZINE	25 25	163	NO
125		SEDATION - VAS	99		1 HYDROXYZINE	25	YES	
.20	Peck et al. (1975)	SEDATION - VAS set of states	99		1 TRIPOLIDINE	1.25	YES	
21	Bye et al. (1974)	SEDATION - VAS	99		1 TRIPOLIDINE	2.5		NO
28	Cohen et al. (1985)	SEDATION - VAS	99		1 TRIPOLIDINE	2.5	YES	
48	Hamilton et al. (1982)	SEDATION - VAS	99		1 TRIPOLIDINE	2.5		NO
76	Nicholson (1979)	SEDATION - VAS	99	9	1 TRIPOLIDINE	2.5	I	NO

82	Nicholson & Stone (1986)	SEDATION - VAS	99	1	TRIPOLIDINE	2.5		NO
21	Bye et al. (1974)	SEDATION - VAS	99	1	TRIPOLIDINE	5	YES	
22	Bye et al. (1977)	SEDATION - VAS	99	1	TRIPOLIDINE	5	YES	
28	Cohen et al. (1985)	SEDATION - VAS	99	1	TRIPOLIDINE	5	YES	
82	Nicholson & Stone (1986)	SEDATION - VAS	99	1	TRIPOLIDINE	5		NO
83	Nicholson et al. (1991)	SEDATION - VAS, Stanford (SSS)	99	1	TRIPOLIDINE	5		NO
91	Peck et al. (1975)	SEDATION - VAS set of states	99	1	TRIPOLIDINE	5	YES	
121	Valk et al. (1997)	SEDATION - Stanford (SSS)	99	1	TRIPOLIDINE	5	YES	
123	Volkerts et al. (1992)	SEDATION - ~VAS (interval scale)	99	1	TRIPOLIDINE	5		NO
117	Swire et al. (1989)	SEDATION - VAS set of states (Bond & Lader)	99	1	TRIPOLIDINE	7.5	YES	
12	Bradley & Nicholson (1986)	SEDATION - VAS Mood assessments	99	1	TRIPOLIDINE	10	YES	
14	Bradley & Nicholson (1987)	SEDATION - VAS Mood assessments	99	1	TRIPOLIDINE	10	YES	
15	Brookhuis et al. (1993)	SEDATION - mental activation (sed)	99	1	TRIPOLIDINE	10		NO
58	Kerr et al. (1994)	SEDATION - VAS	99	1	TRIPOLIDINE	10	YES	
76	Nicholson (1979)	SEDATION - VAS	99	1	TRIPOLIDINE	10		NO
77	Nicholson & Stone (1982)	SEDATION - VAS	99	1	TRIPOLIDINE	10	YES	
78	Nicholson et al. (1982)	SEDATION - VAS	99	1	TRIPOLIDINE	10	1	NO WP
79	Nicholson & Stone (1983)	SEDATION - VAS	99	1	TRIPOLIDINE	10	YES	
80	Nicholson & Stone (1984)	SEDATION - VAS	99	1	TRIPOLIDINE	10	YES	
82	Nicholson & Stone (1986)	SEDATION - VAS	99	1	TRIPOLIDINE	10	YES	
104	Rombaut et al. (1991)	SEDATION - VAS set of states	99	1	TRIPOLIDINE	10	YES	
13A	Bradley et al. (1987)	SEDATION - VAS Mood assessments	99	1	TRIPOLIDINE	10	YES	
13B	Bradley et al. (1987)	SEDATION - VAS Mood assessments	99	1	TRIPOLIDINE	10	YES	and the second se

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cont'd... Sheet: SEDATION

	Sheet: SEDATION							
	Page 2: sorted by Generation, D		ar a x/ ar	9-000000				MENT?
88	Reference	MEASURE of Subjective Sedation	antus.		DRUG	Deserving	88.4.5.38	NO
				2nd	Generation Drugs:			
					· · · · · · · · · · · · · · · · · · ·			
34	Dhorranintra et al. (1986)	SEDATION - VAS & Alertness rating	99	2	ASTEMIZOLE	10		NO
51	Hindmarch & Easton (1986)	SEDATION - VAS set (LARS)	99	2	ASTEMIZOLE	10		NO
77	Nicholson & Stone (1982)	SEDATION - VAS	99	2	ASTEMIZOLE	10		NO
78	Nicholson et al. (1982)	SEDATION - VAS	99	2	ASTEMIZOLE	10		NO
113 114	Seppala & Savolainen (1982)	SEDATION - VAS series	99	2	ASTEMIZOLE	10		NO
77	Simons et al. (1996) Nicholson & Stone (1982)	SEDATION - VAS based on SSS	99	2	ASTEMIZOLE	10		NOWB
113	Seppala & Savolainen (1982)	SEDATION - VAS	99 99	2	ASTEMIZOLE	20 30		NO
25	Chapman & Rawlins (1982)	SEDATION - VAS series	99	2	ASTEMIZOLE ASTEMIZOLE	40		NO NO
44	Gengo et al. (1990)	SEDATION - VAS SEDATION - VAS, Stanford (SSS)	99	2	CETIRIZINE			NO
84	Nicholson & Turner (1998)	SEDATION - VAS, Stanford (SSS)	99	2	CETIRIZINE	5	YES	
111	Seidel et al. (1987)	SEDATION - VAS, Stanford (SSS), POMS	99	2	CETIRIZINE	5		NO
6	Betts et al. (1989)	SEDATION - VAS set	99	2	CETIRIZINE	10		NO
36	Doms et al. (1988)	SEDATION - VAS & ratings	99	2	CETIRIZINE	10		NO
43	Gengo et al. (1987)	SEDATION - VAS	99	2	CETIRIZINE	10		NO
44	Gengo et al. (1990)	SEDATION - VAS, Stanford (SSS)	99	2	CETIRIZINE	10		NO
65	Levander et al. (1991)	SEDATION - VAS; 3/7 sets = sedation	99	2	CETIRIZINE	10		NO
84	Nicholson & Turner (1998)	SEDATION - VAS, Stanford (SSS)	99	2	CETIRIZINE	10	YES	
89	Pechadre et al. (1988)	SEDATION - VAS	99	2	CETIRIZINE	10	1	NO
90	Pechadre et al. (1991)	SEDATION - VAS	99	2	CETIRIZINE	10		NO
95	Ramaekers et al. (1992)	SEDATION - VAS	99	2	CETIRIZINE	10		NO WP
110 · 111	Schweitzer et al. (1994) Seidel et al. (1987)	SEDATION - VAS	99	2	CETIRIZINE	10		NO
114	Simons et al. (1997)	SEDATION - VAS, Stanford (SSS), POMS SEDATION - VAS based on SSS	99 99	2	CETIRIZINE	10	VPO	NO
123	Volkerts et al. (1992)	SEDATION - VAS based of SSS SEDATION - ~VAS (interval scale)	99	2	CETIRIZINE	10 10	YES	10
125	Walsh et al. (1992)	SEDATION - VAS	99	2	CETIRIZINE	10		NO NO WP
6	Betts et al. (1989)	SEDATION - VAS set	99	2	CETIRIZINE	20		NO
33	De Roeck et al. (1990)	SEDATION - Stanford Sleepiness Scale	99	2	CETIRIZINE	20	1	NO?
43	Gengo et al. (1987)	SEDATION - VAS	99	2	CETIRIZINE	20		NO
44	Gengo et al. (1990)	SEDATION - VAS, Stanford (SSS)	99	2	CETIRIZINE	20		NO
84	Nicholson & Turner (1998)	SEDATION - VAS, Stanford (SSS)	99	2	CETIRIZINE	20	YES	
111	Seidel et al. (1987)	SEDATION - VAS, Stanford (SSS), POMS	99	2	CETIRIZINE	20		NO
14	Bradley & Nicholson (1987)	SEDATION - VAS Mood assessments	99	2	LORATADINE	10		NO
37 42	Englisch et al. (1996)	SEDATION - VAS	99	2	LORATADINE	10		NO
57	Gaillard et al. (1988) Kaye et al. (1997)	SEDATION - VAS scales	99	2	LORATADINE	10		NO
75	Neves-Pinto et al. (1992)	SEDATION - Stanford SSS, VAS, Moods SEDATION - reported Sx per list	99 99	2	LORATADINE	10		NO
90	Pechadre et al. (1991)	SEDATION - VAS	99	2	LORATADINE	10 10		NO
95	Ramaekers et al. (1992)	SEDATION - VAS	99	2	LORATADINE	10		NO
109	Schaffler et al. (1994)	SEDATION - VAS; wakefulness	99	2	LORATADINE	10		NO NO
114	Simons et al. (1996)	SEDATION - VAS based on SSS	99	2	LORATADINE	10		NO WB
121	Valk et al. (1997)	SEDATION - Stanford (SSS)	99	2	LORATADINE	10		NO
127	Wilkinson & Moskowitz (1990)	SEDATION - POMS	99	2	LORATADINE	10		NO
133	Corner et al. (1998)	SEDATION - VAS lines in 50 set	99	2	LORATADINE	10		NO
14	Bradley & Nicholson (1987)	SEDATION - VAS Mood assessments	99	2	LORATADINE	20		NO
33	De Roeck et al. (1990)	SEDATION - Stanford Sleepiness Scale	99	2	LORATADINE	20		NO
133 14	Corner et al. (1998) Bradley & Nicholson (1987)	SEDATION - VAS lines in 50 set	99	2	LORATADINE	20		NO
90	Pechadre et al. (1991)	SEDATION - VAS Mood assessments SEDATION - VAS	99	2	LORATADINE	40	1	NO
6	Betts et al. (1989)	SEDATION - VAS	99	2		40		NO
7	Bhatti & Hindmarch (1989)	SEDATION - VAS SE	99 99	2	TERFENADINE	60 60	1	NO
26	Clarke & Nicholson (1978)	SEDATION - VAS	99	2	TERFENADINE	60		NO bP
39	Fink et al. (1979)	SEDATION - Alertness rating	99	2	TERFENADINE	60		NO DP
42	Gaillard et al. (1988)	SEDATION - VAS scales	99	2	TERFENADINE	60		NO
58	Kerr et al. (1994)	SEDATION - VAS	99	2	TERFENADINE	60	1	NO
61 60	Kulshrestha et al. (1978)	SEDATION - VAS for Sedation	99	2	TERFENADINE	60	1	NO
69 71	Meador et al. (1989)	SEDATION - reported occurrences	99	2	TERFENADINE	60	1	NO
71 77	Moser et al. (1978) Nicholson & Stone (1983)	SEDATION - 9-pt VAS: tired, dull	99	2	TERFENADINE	60	1	NO
78	Nicholson & Stone (1982) Nicholson et al. (1982)	SEDATION - VAS	99	2	TERFENADINE	60		NO
79	Nicholson & Stone (1983)	SEDATION - VAS	99	2	TERFENADINE	60	1	NO
82	Nicholson & Stone (1986)	SEDATION - VAS SEDATION - VAS	99	2	TERFENADINE	60		NO
89	Pechadre et al. (1988)	SEDATION - VAS	99 99	2		60 60	1	NO
97	Reinberg et al. (1978)	SEDATION - (~VAS rectangle 22cm)	99	2	TERFENADINE	60 60		NO
114	Simons et al. (1996)	SEDATION - VAS based on SSS	99	2	TERFENADINE	60 60	1	NO 6P NO WB
117	Swire et al. (1989)	SEDATION - VAS set of states (Bond & Lader)	99	2	TERFENADINE	60		NOWB
119	Tharion et al. (1994)	SEDATION - POMS, SX Q	99	2	TERFENADINE	60	1	NO
120	Unchern et al. (1986)	SEDATION - 7-pt ratings & Sx report	99	2	TERFENADINE	60		NO
123	Volkerts et al. (1992)	SEDATION - ~VAS (interval scale)	99	2	TERFENADINE	60		NO
							•	- 1

130A	Witek, Jr. et al. (1992)	SEDATION - VAS (PC), SSS	99	2	TERFENADINE	60	NO
131A	Witek, Jr. et al. (1995)	SEDATION - VAS (PC), SSS	99	2	TERFENADINE	60	NO
6	Betts et al. (1989)	SEDATION - VAS set	99	2	TERFENADINE	120	NO
7	Bhatti & Hindmarch (1989)	SEDATION - VAS	99	2	TERFENADINE	120	NO
71	Moser et al. (1978)	SEDATION - 9-pt VAS: tired, dull	99	2	TERFENADINE	120	NO
74	Murri et al. (1986)	SEDATION - Stanford (SSS)	99	2	TERFENADINE	120	NO
82	Nicholson & Stone (1986)	SEDATION - VAS	99	2	TERFENADINE	120	NO
123	Volkerts et al. (1992)	SEDATION - ~VAS (interval scale)	99	2	TERFENADINE	120	NO
7	Bhatti & Hindmarch (1989)	SEDATION - VAS	99	2	TERFENADINE	240	NO
71	Moser et al. (1978)	SEDATION - 9-pt VAS: tired, dull	99	2	TERFENADINE	240	NO

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Buffer REFERENCE TABLE (# 9 bidgetters BEGATION): TABLE (# 9 bidgetters		sorted by Generation,	Drug, Dose, Ref#, SC#					:	IMPAIRM	
benit (1979) DRIVING SIMULATOR - very basic 15 77 1 CH-COPHENIRAMINE 4 YES 124 Vuuman et al. (1964) DRIVING - Actual, Highway circuit 18 -11/r 1 CLEMASTINE 2 YES 124 Vermeenes & Christion (1988) DRIVING - Actual, Highway circuit 18 -11/r 1 CLEMASTINE 2 YES 124 Cohen et al. (1984) DRIVING - Actual, Highway circuit 18 -11/r 1 DEHENHTORAMINE 50 YES 126 Ramekens et al. (1984) DRIVING - Actual, Car tolowing gest 18 7 1 DI-RENHTORAMINE 50 YES NO 125 Iving & Lones (1982) DRIVING - Actual, Car tolowing gest 17 1 DI-RENHTORAMINE 50 NO 125 Iving & Lones (1982) DRIVING - Actual, Case Concurr 10 Trini 1 TRIPOLIDINE 2.5 NO 126 Iving & Lones (1982) DRIVING - SIMULATOR Sim traffic scenes 17 17 Trini 1 TRIPOLIDINE 5	ROM	REFERENCE	TASK (or Subjective BEDATION)	(er 🐒	16 ST 10 ST 28	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	DRUG	Sussessme	STOCKED BY STOCKED AND	a second second
8 Beni (1979) ORIVING SIMULATOR - very basic 15 77 1 CHCORPHENIRAMINE 4 YES 124 Vurman et al. (1964) DRIVING - Actual, Highway circuit R -1hr 1 CLEMASTINE 3 YES NO 27 Cohen et al. (1964) DRIVING - Actual, Highway circuit R -1hr 1 CLEMASTINE 3 NO 46 Gergo et al. (1964) DRIVING - Actual, Agrinywy circuit 1C 15 rin 1 DIFHENHORAMINE 50 YES NO 47 Cohen et al. (1964) DRIVING - Actual, Agrinywy circuit 1C 15 rin 1 DIFHENHORAMINE 50 YES 48 Ramekers et al. (1964) DRIVING - MARU, Carl toxens 17 DIFHENHORAMINE 50 YES NO 51 Iring & Jone (1922) DRIVING - MARU, Carl toxens 17 DIFHENHORAMINE 50 NO 55 Iring & Jone (1922) DRIVING - MARU, Carl toxens 17 DIFHENHORAMINE 50 NO 56 Iring & Jone										
12.2 Vurman et al. (1994) DRIVING - Actual, Highwey grout 17.						1st	Generation Drugs:			
12.2 Vurman et al. (1994) DRIVING - Actual, Highwey grout 17.	8	Riehl (1979)	DRIVING SIMULATOR - very basic	18	~~~~	1		4	YES	
112 Vermeens af, (1964) DRIVING - Actual, Highway orout 17 1 CLEMASTINE 3 YES 27 Cohen et al, (1984) DRIVING - off-cad, circuit 17 1 DIPEEM-MYDRAMINE 50 NO 46 Gengo et al, (1990) DRIVING - Actual, Carbitoving test 17 1 DIPEEM-MYDRAMINE 50 YES 56 Rameeters et al, (1994) DRIVING - Actual, Carbitoving test 17 1 DIPEEM-MYDRAMINE 50 YES 77 Cohen et al, (1984) DRIVING - Actual, Carbitoving test 17 1 TIRIPOLIDINE 2.5 NO 55 Iving & Jones (1982) DRIVING - Actual, Clease Concert 15 1									11	
27 Cohen et al. (1984) DRIVING - offraad, circuit 1C 15 IDPEENHYDRAMINE 25 NO 44 Gengo et al. (1984) DRIVING - offraad, circuit 1C 15 7m in runs 1 DIPEENHYDRAMINE 50 YES 66 Ramesters et al. (1984) DRIVING - Actual, Catabony feet 1R -11 1 DIPEENHYDRAMINE 50 YES 72 Cohen et al. (1984) DRIVING - Actual, Catabony feet 1R -11 1 DIPEENHYDRAMINE 50 YES 72 Cohen et al. (1984) DRIVING - Actual, Catabony feet 1R -11 1 <td></td> <td></td> <td></td> <td></td> <td>ł.</td> <td></td> <td></td> <td></td> <td>11</td> <td></td>					ł.				11	
27 Cohen et al. (1984) DRIVING - off-oad, circuit. 10 DIPER-IMPORAINE 50 NO 86 Ramekers et al. (1994) DRIVING - Actual, Carbioving test. 17 17 10 <										NO
4. Comport at (1990) DPIVING SIMULATOR - Doron, 2 dift, runs, 15 7 min runs, 1 DPI-EN-MORAMINE 50 YES 96 Rameelens et at (1994) DRIVING - Aduat, 4 rightwoy circuit 17 1 DIPI-EN-MORAMINE 50 VIS 97 Cohen et at (1964) DRIVING - Aduat, 4 rightwoy circuit 17 1 DIPI-EN-MORAMINE 50 NO 55 Inring & Jones (1992) SPEED PERCEPTION - Sim traffic scenes 17 12 min / 1 TRIPOLIDINE 2.5 NO 55 Inring & Jones (1992) DRIVING - Aduat, Closed course 17 12 min / 1 TRIPOLIDINE 2.5 NO 55 Inring & Jones (1992) DRIVING - Aduat, Closed course 17 12 min / 1 TRIPOLIDINE 5 NO 51 Inring & Jones (1992) DRIVING - Aduat, Closed course 10 15 fism in 1 TRIPOLIDINE 5 NO 121 Valket at (1967) Mul-Attribute Task Ratery (MAT) - on FC 18 10 min 1 TRIPOLIDINE 5 NO 121 Valket at (1968) DRIVING - Aduat										
66 Rameson et al. (1994) DRIVING - Adual, Car following test 17 12 min 1 DIPHENH/TGRAMINE 50 YES 96 Rameson et al. (1994) DRIVING - Adual, Hojhway circuit 17 12 min 1 DIPHENH/TGRAMINE 50 NO 55 Inving & Jones (1992) BRIVING - Adual, Hojhway circuit 17 12 min 1 TRIPLOIDINE 2.5 NO 55 Inving & Jones (1992) DRIVING - Adual, Coste course 17 12 min 1 TRIPLOIDINE 2.5 NO 56 Inving & Jones (1992) DRIVING - Matual, Coste course 17 12 min 1 TRIPLOIDINE 5.5 NO 55 Inving & Jones (1992) DRIVING - Matual, Coste course 17 12 min 1 TRIPLOIDINE 5 NO 51 Infig & Jones (1992) DRIVING - Adual, Highway circuit 18 1 1 TRIPLOIDINE 5 NO 12 Valket al. (1963) DRIVING - Adual, Highway circuit 18 1 1 1 1					14				YES	
9 Remembers et al. (1994) DRIVING - Aduat, Highway circuit 10 -11r 1 DIFIENT/GRAMINE 50 YES 27 Cohen et al. (1984) DRIVING - Aduat, Highway circuit 17 12 17					1				8	
27 Cohen et al. (1994) DRIVING - off-oad, arout 10 11 DIFFUND CANCER NO 55 Ining & Jones (1982) HAZARD PERCEPTION - Sim traffic scenes 12 12 12 11 <td< td=""><td></td><td></td><td></td><td></td><td>K</td><td></td><td></td><td></td><td></td><td></td></td<>					K					
55 rving 4 Jones (1992) H4ZARD PERCEPTION - Sim traffic scenes 17 12 rinfo 1 TRIPOLIDINE 2.5 NO 55 rving 4 Jones (1982) DRVING - Actual, Closed course 17 13 17					1				120	NO
55 Iving & Jones (1992) SPEED PERCEPTION - Sim taffic scenes 17 12 min 1 TRIPOLIDINE 2.5 NO 55 Iving & Jones (1992) DRIVING - Adual, Cload course 15 15 min 1 TRIPOLIDINE 2.5 NO 55 Iving & Jones (1992) DRIVING - SMULLATOR 15 15 min 1 TRIPOLIDINE 5 NO 55 Iving & Jones (1992) DRIVING - Adual, Cload course 17 12 min 1 TRIPOLIDINE 5 NO 55 Iving & Jones (1992) DRIVING - Adual, Highwey incut 15 15 min 1 TRIPOLIDINE 5 NO 121 Valent et al. (1992) DRIVING - Adual, Highwey incut 18 17 min 1 TRIPOLIDINE 5 NO 15 Brothwise et al. (1993) DRIVING - Adual, Highwey incut 18 17 min 1 TRIPOLIDINE 10 YES 54 Orhent at (1990) DRIVING - Adual, Agna sceptance 16 7 min mas 2 CETRZINE 10 YES NO 54 Bertis et al. (1980) DRIVING S Adual, Agna sceptance		· · ·								11
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YES: Summary: 1st generation drugs; 47.83%			\$		1		Summan: 1et comm	tion druge:	•	

Summary: 1st generation drugs: 47.83% 2nd generation drugs: 12.50% ,

Sheet: Psychomotor TABLE 6. PSYCHOMOTOR TASKS - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only

Eds. Description Test	Page 2 s	orted by Generation, DRUG, Dos	e. Ref#. SC#.					1	IMPAIRM	AENT?
8 Behr (1979) FINGET PropNic 27 Sole 1 ChCRPHENIXAMINE 4 YES MO 60 Forda et al. (1978) Cale Back Packing (opcorek-rotor) 20 Intel al. (1978) Cale Back Packing (opcorek-rotor) 1 ChCRPHENIXAMINE 4 YES YES 10 Luchem et al. (1978) Fanda et al. (1979) Fanda et al. (1978) Fanda et al. (1978) <t< th=""><th></th><th></th><th>ТАВК</th><th>8. (<u>e.</u> 8</th><th></th><th></th><th>ondio .</th><th></th><th></th><th></th></t<>			ТАВК	8. (<u>e.</u> 8			ondio .			
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35 Dommins et (1978) Came Base Polong (percept-motor) 20 order 1 OLCORPRENENAMINE 4 YES 40 Prenise et (1978) STACING STEADRESS 28 1 OLCORPRENAMINE 4 YES 41 Prenise et (1978) STACING STEADRESS 28 1 OLCORPRENAMINE 4 YES 120 Unorem et (1980) Pred Basel (1977) MALL DEXTEMPTY 20 OLCORPRENAMINE 1 OLCORPRENAMINE 1 NO 120 Unorem et (1980) Pred Basel (1970) MALL DEXTEMPTY 20 OLCORPRENAMINE 1 VES 130 Day et al. (1972) MACL-SE CORDINATION 2 Mol CLEMASTRE 1 NO 14 Fernise et al. (1972) MACL-SE CORDINATION 2 Mol CLEMASTRE 1 NO 15 Day et al. (1972) MACL-SE CORDINATION 2 Mol CLEMASTRE 1 NO 16 Reading et al. (1972) MACL-SE CORDINATION 2 Mol CLEMASTRE	9	Right (1070)		27	30600		-	4	YES	
40 Paraba et al. (1979) Viera Oxemination Appantisus 27 1 CHCRPHENRAMME 4 YES 40 Frans et al. (1979) MANUAL SCHEMTY 20 Discussion 4 YES No 40 Frans et al. (1979) MANUAL SCHEMTY 20 Discussion 4 YES No 51 Witk, J. et al. (1980) Frans et al. (1979) Frans et al. (1978) Fra										NO
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30 Curran et al. (1989) DIOT CANCELLATION 2 Dief 1 DIPERINTORAMINE 25 NO 30 Curran et al. (1986) Pikag Baard (put pirs in holes) 20 20 ase /2 1 DIPERINTORAMINE 25 NO 310 Witek, et al. (1987) FINAGER TAPPING 27 2 min DIPERINTORAMINE 25 NO 311 Witek, et al. (1987) FINAGER TAPPING 27 2 min DIPERINTORAMINE 50 NO 312 Corten et al. (1987) FINAGER TAPPING 27 2 min DIPERINTORAMINE 50 NO 313 Corten et al. (1987) BODY SWAY - antero-potetric 28 3 min DIPERINTORAMINE 50 NO 32 Corten et al. (1987) FINAGER TAPPING antero potetric 28 3 min DIPERINTORAMINE 50 NO 330 Curran et al. (1987) FINAGER TAPPING antero potetric 28 No 1 DIPERINTORAMINE 50 NO 330 Minet al. (1987) FIN			· ·		11	-			1	NO
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2 Cambra et al. (1976) FINGER TAPENAS T 60 ase: 1 DIPEENMORAMINE 50 NO 27 Cohen et al. (1987) BODY SWAY - anter-spontenor 28 2 min 1 DIPEENMORAMINE 50 NO 30 Curran et al. (1996) SYMBOL COPYING - motor comp of DSST 2 0 ase: 1 DIPEENMORAMINE 50 NO 30 Curran et al. (1996) FINGER TAPPING 27 5 divert 1 DIPEENMORAMINE 50 NO 30 Curran et al. (1996) FINGER TAPPING 27 5 divert 1 DIPEENMORAMINE 50 YES 3136 Witek, at et al. (1992) Hand Steadinese (FC) 28 b, brief 1 DIPEENMORAMINE 50 YES 3138 Witek, at et al. (1982) Hand Steadinese (FC) 28 b, brief 1 DIPEENMORAMINE 50 YES 3138 Witek, at et al. (1982) BALANCE - Time keep for nised; eyes cload 29 3 nin<1					8				YES	NO
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30 Curran et al. (1998) DIGIT CANCELLATION 2 order 1 DIPLENHYDRAIINE 50 NO 30 Curran et al. (1998) SYMBOL COPYING - motor comp of DSST 2 80 eco 1 DIPLENHYDRAIINE 50 NO 30 Curran et al. (1998) FINGER TAPPING 2 80 eco 1 DIPLENHYDRAIINE 50 NO 316 Spector et al. (1980) FINGER TAPPING - atternating area 27 3 Other 1 DIPLENHYDRAIINE 50 NO 3130 Witek, Jr. et al. (1980) Hand Steadinese (PC) 28 V. brief DIPLENHYDRAIINE 50 YES 3131 Witek, Jr. et al. (1986) Hand Steadinese (PC) 28 Norief DIPLENHYDRAIINE 50 YES 3131 Witek, Jr. et al. (1986) BALANCE - Trae keep foot raised; eyes closed 28 Norief DIPLENHYDRAIINE 50 NO 34 Witek Jr. et al. (1972) BALANCE - Trae keep foot raised; eyes closed 28 2 7111 DIPLENHYDRAIINE 100 NO			2	8	n ·					NO
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94 Preston et al. (1992) BALANCE - Time keep foot raised; eyes closed 2B 2 min 1 DIPHENHYDRAMINE 100 NO 106 Saaraiho-Kere et al. (1989) Preston et al. (1980) BALANCE - Time keep foot raised; eyes closed 2B 2 min 1 DIPHENHYDRAMINE 100 NO 94 Preston et al. (1985) FINGER TAPPING - index; attemating 2 fingers T min DIPHENHYDRAMINE 200 NO 94 Preston et al. (1982) FINGER TAPPING - index; attemating 2 fingers T min DIPHENHYDRAMINE 200 YES 65 Levender et al. (1982) FINGER TAPPING index; attemating 2 fingers 2T min T Trimin TIPOLIDINE 2.5 YES 78 Nichoison & Stone (1984) FINGER TAPPING 2T finin T TIPOLIDINE 10 YES 78 Nichoison & Stone (1986) StMBOL COPYING - motor comp of DSST 2 finin T TIPIPOLIDINE 10 YES 74 Nichoison & Stone (1986) StMBOL COPYING - isterial & segitt			· · ·		н	1	DIPHENHYDRAMINE	100	YES	
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106 Saaralho-Kere et al. (1980) FINGER TAPPING 2T 1 min 1 DIPHENHYDRAMINE 100 NO 94 Preston et al. (1982) FINGER TAPPING - index; atternating 2 fingers 2T 1 min 1 DIPHENHYDRAMINE 200 YES 65 Levander et al. (1985) FINGER TAPPING - index; atternating 2 fingers 2T v. brief 1 HYDRXX2INE 20 NO 21 Byset al. (1974) FINGER TAPPING FINGER TAPPING 2T v. brief 1 HYDRXX2INE 20 NO 21 Byset al. (1974) FINGER TAPPING FINGER TAPPING 2T 60 sec 1 TRIPOLIDINE 25 YES 28 Vet al. (1974) FINGER TAPPING FINGER TAPPING 2T 60 sec 1 TRIPOLIDINE 5 YES 78 Nicholson et al. (1986) CANCELLATION Task. (P&P. letters) 2 5 min 1 TRIPOLIDINE 10 NO 78 Nicholson et al. (1986) Glass Beed Picking (percept-motor) 20 brief 2 ASTEMIZOLE 10 NO 78 Sex		• •		K						
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71Moser et al. (1978)PSYCHOMOTOR TASKS (set of 5)22TERFENADINE60NO78Nicholson et al. (1982)CANCELLATION Task - (P&P, letters)25 min2TERFENADINE60NO82Nicholson & Stone (1986)SYMBOL COPYING - motor comp of DSST21 min2TERFENADINE60NO97Reinberg et al. (1978)EYE-HAND SKILL Test (bearings in tube)2Dv. brief2TERFENADINE60NO120Unchem et al. (1986)Plug Board (put pins in holes)2D2D sec x22TERFENADINE60NO130AWitek, Jr. et al. (1992)Hand Steadiness (PC)2Bv. brief2TERFENADINE60NO131AWitek, Jr. et al. (1978)PSYCHOMOTOR TASKS (set of 5)22TERFENADINE60NO71Moser et al. (1978)PSYCHOMOTOR TASKS (set of 5)22TERFENADINE120NO82Nicholson & Stone (1986)SYMBOL COPYING - motor comp of DSST21 min2TERFENADINE120NO			1	10	?				1	
78Nicholson et al. (1982)CANCELLATION Task - (P&P, letters)25 min2TERFENADINE60NO82Nicholson & Stone (1986)SYMBOL COPYING - motor comp of DSST21 min2TERFENADINE60NO97Reinberg et al. (1978)EYE-HAND SKILL Test (bearings in tube)2Dv. brief2TERFENADINE60NO120Unchem et al. (1986)Plug Board (put pins in holes)2D20 sec x22TERFENADINE60NO130AWitek, Jr. et al. (1992)Hand Steadiness (PC)2Bv. brief2TERFENADINE60NO131AWitek, Jr. et al. (1978)PSYCHOMOTOR TASKS (set of 5)222TERFENADINE60NO82Nicholson & Stone (1986)SYMBOL COPYING - motor comp of DSST21 min2TERFENADINE120NO				11	v. brief					
82Nicholson & Stone (1986)SYMBOL COPYING - motor comp of DSST21 min2TERFENADINE60NO97Reinberg et al. (1978)EYE-HAND SKILL Test (bearings in tube)2Dv. brief2TERFENADINE60NO120Unchem et al. (1986)Plug Board (put pins in holes)2D20 sec x22TERFENADINE60NO130AWitek, Jr. et al. (1992)Hand Steadiness (PC)2Bv. brief2TERFENADINE60NO131AWitek, Jr. et al. (1995)Hand Steadiness (PC)2Bv. brief2TERFENADINE60NO71Moser et al. (1978)PSYCHOMOTOR TASKS (set of 5)222TERFENADINE120NO82Nicholson & Stone (1986)SYMBOL COPYING - motor comp of DSST21 min2TERFENADINE120NO		, ,			5	-				
97Reinberg et al. (1978)EYE-HAND SKILL Test (bearings in tube)2Dv. brief2TERFENADINE60NO120Unchern et al. (1986)Plug Board (put pins in holes)2D20 sec x22TERFENADINE60NO130AWitek, Jr. et al. (1992)Hand Steadiness (PC)2Bv. brief2TERFENADINE60NO131AWitek, Jr. et al. (1995)Hand Steadiness (PC)2Bv. brief2TERFENADINE60NO71Moser et al. (1978)PSYCHOMOTOR TASKS (set of 5)22TERFENADINE120NO82Nicholson & Stone (1986)SYMBOL COPYING - motor comp of DSST21 min2TERFENADINE120NO					1					
120Unchem et al. (1986)Piug Board (put pins in holes)2D2D20 sec x22TERFENADINE60NO130AWitek, Jr. et al. (1992)Hand Steadiness (PC)2Bv. brief2TERFENADINE60NO131AWitek, Jr. et al. (1995)Hand Steadiness (PC)2Bv. brief2TERFENADINE60NO71Moser et al. (1978)PSYCHOMOTOR TASKS (set of 5)22TERFENADINE120NO82Nicholson & Stone (1986)SYMBOL COPYING - motor comp of DSST21 min2TERFENADINE120NO		• •		13	11					
130AWitek, Jr. et al. (1992)Hand Steadiness (PC)2Bv. brief2TERFENADINE60NO131AWitek, Jr. et al. (1995)Hand Steadiness (PC)2Bv. brief2TERFENADINE60NO71Moser et al. (1978)PSYCHOMOTOR TASKS (set of 5)22TERFENADINE120NO82Nicholson & Stone (1986)SYMBOL COPYING - motor comp of DSST21 min2TERFENADINE120NO					R					
131AWitek, Jr. et al. (1995)Hand Steadiness (PC)2Bv. brief2TERFENADINE60NO71Moser et al. (1978)PSYCHOMOTOR TASKS (set of 5)22TERFENADINE120NO82Nicholson & Stone (1986)SYMBOL COPYING - motor comp of DSST21 min2TERFENADINE120NO		• •		H I	#				1	
71Moser et al. (1978)PSYCHOMOTOR TASKS (set of 5)22TERFENADINE120NO82Nicholson & Stone (1986)SYMBOL COPYING - motor comp of DSST21 min2TERFENADINE120NO		, , ,	1 · ·		i l					
82 Nicholson & Stone (1986) SYMBOL COPYING - motor comp of DSST 2 1 min 2 TERFENADINE 120 NO				8	1				ļ	
71 Moser et al. (1978) PSYCHOMOTOR TASKS (set of 5) 2 TERFENADINE 240 NO			2		1 min					
	71	Moser et al. (1978)	PSYCHOMOTOR TASKS (set of 5)	2		2	TERFENADINE	240	٤	NO

SC#3

Page 2: sorted by Generation, DRUG, Dose, Ref#, SC#.

Page 2. solice by Generation, DNOG, Dose, New, Com.								IMPAIR	
	REPRESE	TASK	8.ie. 8	Department		DRUG	Stational S	ale a	
					1st	Generation Drugs:			
8	Biehl (1979)	TACHISTOSCOPE - 4 slides of 16 ltrs	3	very brief	1	CHLORPHENIRAMINE	4		NO
	Franks et al. (1978)	PERCEPTUAL SPEED	3		1	CHLORPHENIRAMINE	4		NO
	Franks et al. (1979)	PERCEPTUAL SPEED	3	1	1	CLEMASTINE	1		NO
	Seppala et al. (1981)	TIME ANTICIPATION - Est speed of moving light	37	v. brief	1	CLEMASTINE	1		NO
	Seppaia et al. (1981)	VISUAL SEARCH - (they say "D-A"?)	3VS	5 min	1	CLEMASTINE	1		NO
	Katz et al. (1998)	Pattern Recognition - spatial perception	3	brief	1	DIPHENHYDRAMINE	25	[NO
	Burns & Moskowitz (1993)	VISUAL SEARCH - SCRI	3VS	6 min	1	DIPHENHYDRAMINE	25	YES	
	Burns & Moskowitz (1993)	VISUAL SEARCH - SCRI	3VS	6 min	1	DIPHENHYDRAMINE	25		NÒ
	Moskowitz & Burns (1988)	VISUAL SEARCH - SCRI	3VS	6 min	1	DIPHENHYDRAMINE	50	YES	
	Sands et al. (1997)	Pattern Recognition - spatial perception	3?	brief	1	DIPHENHYDRAMINE	50	YES	
	Sands et al. (1997)	Pattern Recognition - spatial perception	37	brief	1	DIPHENHYDRAMINE	75	YES	
	Mohs et al. (1978)	TIME PRODUCTION Task (time estimates)	3	5-10 min	1	DIPHENHYDRAMINE	100	YES	
	Mohs et al. (1978)	VISUAL SEARCH (t-scope, digits)	378	20 min	1	DIPHENHYDRAMINE	100		NO
	Saarialho-Kere et al. (1989)	VISUAL SEARCH - (they say "D-A"?)	3VS	5 min	1	DIPHENHYDRAMINE	100		NO
21	Bye et al. (1974)	VISUAL SEARCH	378	30 min	1	TRIPOLIDINE	2.5	1	NO
	Bye et al. (1974)	VISUAL SEARCH	378	30 min	1	TRIPOLIDINE	5	1	NO
	Volkerts et al. (1992)	Visual Discrimination (Letter or Digit)	3	~10 min	1	TRIPOLIDINE	5	YES	
					2nd	Generation Drugs:			
113	Seppala & Savolainen (1982)	TIME ANTICIPATION - Est speed of moving light	37	v. brief	2	ASTEMIZOLE	10		NO
	Seppala & Savolainen (1982)	TIME ANTICIPATION - Est speed of moving light	3?	v. brief	2	ASTEMIZOLE	30		NO
123	Volkerts et al. (1992)	Visual Discrimination (Letter or Digit)	3	~10 min	2	CETIRIZINE	10		NO
73	Moskowitz & Burns (1988)	VISUAL SEARCH - SCRI	378	6 min	2	TERFENADINE	60		NO PI
123	Volkerts et al. (1992)	Visual Discrimination (Letter or Digit)	3	~10 min	2	TERFENADINE	60	1	NO
18A	Burns & Moskowitz (1993)	VISUAL SEARCH - SCRI	378	6 min	2	TERFENADINE	60		NO
188	Burns & Moskowitz (1993)	VISUAL SEARCH - SCRI	378	6 min	2	TERFENADINE	60		NO
123	Volkerts et al. (1992)	Visual Discrimination (Letter or Digit)	3	~10 min	2	TERFENADINE	120		NO
188	Burns & Moskowitz (1993)	VISUAL SEARCH - SCRI	3VS	6 min	2	TERFENADINE	120		NO

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VISUAL FUNCTIONS TABLE 8A.

Page 2: sorted by SC#, Generation, DRUG, Dose, Ref#

9000- 100- ··· 000			/					IMPAIR	MENT?
Reff	Reference	TASK (or Subjective SEDATION)	S. C.S.	20120100	: Ca	(DhUIG)	Medical Nation		
						•			
					150	Generation Drugs:			
31	Day et al. (1972)	VISUAL FUNCTION TESTS (5 types)	4		1	CLEMASTINE	1		NO
29	Cohen et al. (1987)	SACCADIC EYE MOVEMENTS	4	-5 min?	, 1	DIPHENHYDRAMINE	50	YES	NO
29	Cohen et al. (1987)	SMOOTH PURSUIT EYE MOVEMENTS	4	-5 min?	1	DIPHENHYDRAMINE	50	120	NO
68	Mattila et al. (1986)	MADDOX WING (extraocular muscles)	4	v. brief	1	DIPHENHYDRAMINE	100		NOWB
106	Saarialho-Kere et al. (1989)	MADDOX WING (extraocular muscles)	4	v. brief	1	DIPHENHYDRAMINE	100		NO
9	Blom et al. (1992)	SACCADIC EYE MOVEMENT - SEM-K	4		1	HYDROXYZINE	30	YES	
12	Bradley & Nicholson (1986)	DYNAMIC VISUAL ACUITY	4	~5 min	1	TRIPOLIDINE	10	YES	
14	Bradley & Nicholson (1987)	DYNAMIC VISUAL ACUITY	4	~5 min	1	TRIPOLIDINE	10	YES	
78	Nicholson et al. (1982)	DYNAMIC VISUAL ACUITY - DVA (Landoit C rings)	4	v. brief	1	TRIPOLIDINE	10	YES	
78	Nicholson et al. (1982)	PUPILLARY DIAMETER (TV pupillometer)	4	v. brief	1	TRIPOLIDINE	10		NO
79	Nicholson & Stone (1983)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	1	TRIPOLIDINE	10	YES	
80	Nicholson & Stone (1984)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	1	TRIPOLIDINE	10	YES	
82	Nicholson & Stone (1986)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	1	TRIPOLIDINE	10	YES	
13A	Bradley et al. (1987)	DYNAMIC VISUAL ACUITY	4	~5 min	1	TRIPOLIDINE	10	YES '	
13B	Bradley et al. (1987)	DYNAMIC VISUAL ACUITY	4	~5 min	1	TRIPOLIDINE	10	YES	
				1					
	1				2nd	Generation Drugs:			
78	Nicholson et al. (1982)	DYNAMIC VISUAL ACTIVE DVA (Landah China)							
78	Nicholson et al. (1982)	DYNAMIC VISUAL ACUITY - DVA (Landoit C rings) PUPILLARY DIAMETER (TV pupiliometer)	4	v. brief	2	ASTEMIZOLE	10		NO
6	Betts et al. (1989)	VISION TEST (Visual field index)	4	v. brief	2 2	ASTEMIZOLE	10		NO
6	Betts et al. (1989)	VISION TEST (Visual field index)	4		2	CETIRIZINE	10		NO
14	Bradley & Nicholson (1987)	DYNAMIC VISUAL ACUITY	4	~5 min	2	LORATADINE	20 10		NO
37	Englisch et al. (1996)	VISUAL FUNCTIONS - in Oculodynamic test	4	20 min	2	LORATADINE	10	ļ	NO
109	Schaffler et al. (1994)	Oculodynamic Test (ODT)- EOG measures	4	20 min	2	LORATADINE	10		NO
14	Bradley & Nicholson (1987)	DYNAMIC VISUAL ACUITY	4	~5 min	2	LORATADINE	20	ļ	NO
14	Bradley & Nicholson (1987)	DYNAMIC VISUAL ACUITY	4	~5 min	2	LORATADINE	20 40	YES	NO
6	Betts et al. (1989)	VISION TEST (Visual field index)	4		2	TERFENADINE	40 60	153	
78	Nicholson et al. (1982)	PUPILLARY DIAMETER (TV pupillometer)	4	v. brief	2	TERFENADINE	60		NO NO
78	Nicholson et al. (1982)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	2	TERFENADINE	60		NO
79	Nicholson & Stone (1983)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	2	TERFENADINE	60		NO
82	Nicholson & Stone (1986)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	2	TERFENADINE	60		NO
6	Betts et al. (1989)	VISION TEST (Visual field index)	4		2	TERFENADINE	120		NO
82	Nicholson & Stone (1986)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	2	TERFENADINE	120		NO

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SC#4 VISUAL FUNCTIONS & CFF - Summary of Impairment findings as a function of DRUG and Dose - ACUTE DOSING only

Sheet: VISUAL_CFF continued...

CRITICAL FLICKER FUSION

TABLE 8B.

	Page 2: sorted by SC#, Genera	IION, UKUG, UOSE, KET#						IMPAIRM	MENT?
Rent		TASK (or Subjective SEDATION)	\$ Ye . \$	Duration	en	DRUG	Dose mg	NIEGO.	
2000									
				1	st	Generation Drugs:			
64	Kulehmethe et al. (1978)	CRITICAL FLICKER FUSION - CFF	4C	v, brief	1	CHLORPHENIRAMINE	4		NO
61 63	Kuishrestha et al. (1978) Lee et al. (1988)	CRITICAL FLICKER FUSION - CFF				CHLORPHENIRAMINE	12	ļ	NO
59	Khosla et al. (1993)	CRITICAL FLICKER FUSION (CFF)	8			CHLORPHENIRAMINE	16		NO WB
		CRITICAL FLICKER FUSION - CFF	11	8		CLEMASTINE	1		NO
93	Pishkin et al. (1983)	CRITICAL FLICKER FUSION - CFF	11			CLEMASTINE	1		NO
112	Seppala et al. (1981)	CRITICAL FLICKER FUSION - CFF	μ			CLEMASTINE	2	YES	
87	Patat et al. (1994) Displiis et al. (1983)	CRITICAL FLICKER FUSION - CFF	40	1		CLEMASTINE	2		NO
93	Pishkin et al. (1983)	CRITICAL FLICKER FUSION - CFF	40	8		CLEMASTINE	2	YES	
124	Vuurman et al. (1994)	CRITICAL FLICKER FUSION - CFF	40	<u>u</u>		DIPHENHYDRAMINE	25		NO
30 30	Curran et al. (1998) Curran et al. (1998)	CRITICAL FLICKER FUSION - CFF	40	H	1	DIPHENHYDRAMINE	50		NO
39	Fink et al. (1979)	CRITICAL FLICKER FUSION - CFF	1 ·		1	DIPHENHYDRAMINE	50		NO
93	Pishkin et al. (1983)	CRITICAL FLICKER FUSION - CFF	40	9	1	DIPHENHYDRAMINE	50		NO
119	Tharion et al. (1994)	CRITICAL FLICKER FUSION - CFF	40	11	1	DIPHENHYDRAMINE	50	1	NO
	Mattila et al. (1986)	CRITICAL FLICKER FUSION - CFF	40	H	1	DIPHENHYDRAMINE	100	YES	
68 71	Moser et al. (1978)	CRITICAL FLICKER FUSION - CFF	40	H	1	DIPHENHYDRAMINE	100		NO
106	Saarialho-Kere et al. (1989)	CRITICAL FLICKER FUSION - CFF	40	v. brief	1	DIPHENHYDRAMINE	100	YES	
43	Gengo et al. (1987)	CRITICAL FLICKER FUSION - CFF	40		1	HYDROXYZINE	25	YES	
93	Pishkin et al. (1983)	CRITICAL FLICKER FUSION - CFF	4C	v, brief	1	HYDROXYZINE	25	1	NO
9	Blom et al. (1992)	CRITICAL FLICKER FUSION	4C		1	HYDROXYZINE	30		NO
117	Swire et al. (1989)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	TRIPOLIDINE	7.5	YES	
12	Bradley & Nicholson (1986)	CRITICAL FLICKER FUSION - CFF	4C	~5 min	1	TRIPOLIDINE	10	YES	
58	Kerr et al. (1994)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	TRIPOLIDINE	10	YES	
78	Nicholson et al. (1982)	CRITICAL FLICKER FUSION - CFF	40	v. brief	1	TRIPOLIDINE	10	YES	
79	Nicholson & Stone (1983)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	TRIPOLIDINE	10	YES	
80	Nicholson & Stone (1984)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	TRIPOLIDINE	10	YES	
82	Nichoison & Stone (1986)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	TRIPOLIDINE	10	YES	
104	Rombaut et al. (1991)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	TRIPOLIDINE	10	YES	
13A	Bradley et al. (1987)	CRITICAL FLICKER FUSION - CFF	4C	~5 min	1	TRIPOLIDINE	10	YES	
13B	Bradiey et al. (1987)	CRITICAL FLICKER FUSION - CFF	4C	~5 min	1	TRIPOLIDINE	10	YES	
				:	2nd	Generation Drugs:			
51	Hindmarch & Easton (1986)	CRITICAL FLICKER FUSION - CFF	40	v. brief	2	ASTEMIZOLE	10	1	NO
78	Nicholson et al. (1982)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	ASTEMIZOLE	10		NO
113	Seppala & Savolainen (1982)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	ASTEMIZOLE	10		NO
113	Seppala & Savolainen (1982)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	ASTEMIZOLE	30		NO
43	Gengo et al. (1987)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	CETIRIZINE	10		NC
100	Riedel et al. (1990)	CRITICAL FLICKER FUSION - CFF	40		2	CETIRIZINE	10		NC
43	Gengo et al. (1987)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	CETIRIZINE	20		NC
100	Riedel et al. (1990)	CRITICAL FLICKER FUSION - CFF	4C		2	CETIRIZINE	20		NC
7	Bhatti & Hindmarch (1989)	CRITICAL FLICKER FUSION (CFF)	40	very brief	2	TERFENADINE *	60		NC
39	Fink et al. (1979)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60		NC
58	Kerr et al. (1994)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60	YES	
61	Kulshrestha et al. (1978)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60		NC
71	Moser et al. (1978)	CRITICAL FLICKER FUSION - CFF	40	v. brief	2	TERFENADINE	60		NC
78	Nicholson et al. (1982)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60		NC
79	Nicholson & Stone (1983)	CRITICAL FLICKER FUSION - CFF	40	v. brief	2	TERFENADINE	60		NC
82	Nicholson & Stone (1986)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60		NC
117		CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60	1	NC
124		CRITICAL FLICKER FUSION - CFF	4C	6 mln	2	TERFENADINE	60		NO
7	Bhatti & Hindmarch (1989)	CRITICAL FLICKER FUSION (CFF)	4C	very brief	2	TERFENADINE	120		NC
71 82	Moser et al. (1978) Nicholson & Stone (1986)	CRITICAL FLICKER FUSION - CFF	4C	11	2	TERFENADINE	120		NC
	Nicholson & Stone (1986)	CRITICAL FLICKER FUSION - CFF	4C		2		120		NK
	Dhatti 9 Lindmarch (4000)								
7 71	Bhatti & Hindmarch (1989) Moser et al. (1978)	CRITICAL FLICKER FUSION (CFF) CRITICAL FLICKER FUSION - CFF	4C 4C	14 ·	2	TERFENADINE	240 240		

SC#5 Page 2: sorted by Generation, DRUG, Dose, Ref#, SC#.

TABLE 9.

								IMPAIR	
.C. 8	REFERENCE	TASK (or Subjective SEDATION)	8./ri.#	Duration		ORUG			I NK
					1st	Generation Drugs:			
						· ·			
8	Biehl (1979)	CONCENTRATION TEST (KLT) - math		15 min	1	CHLORPHENIRAMINE	4	1	NC
35	Dhorranintra et al. (1990)	CARD SORTING test (CNS problem solving)	5	brief	1	CHLORPHENIRAMINE	4		NC
40	Franks et al. (1978)		5	. brint	1	CHLORPHENIRAMINE	4	YES	
120 120	Unchern et al. (1986)	Arithmetic (p&p ??)	5 5	v. brief	1	CHLORPHENIRAMINE	4	YES	NC
120	Unchern et al. (1986)	Card Sorting Task (4 piles #1-10 each) Digit Span ("Recall Memory; F & Backward)	5 5M	v. brief v. brief	1		4	TES	NO
120	Unchern et al. (1986) Unchern et al. (1986)		5M 5T	30sec X2	1	CHLORPHENIRAMINE	4	YES	140
120	Unchern et al. (1986)	Line Test (p&p: draw ~= tracking) T-Maze (p&p: draw ~= tracking)	51 5T	30sec A2	1	CHLORPHENIRAMINE	4	IEO	NO
131B		DIGIT SYMBOL Substitution - DSST	5D	2 min	1	CHLORPHENIRAMINE	4		N
83	Witek, jr. et al. (1995) Nicholson et al. (1991)	DIGIT SYMBOL Substitution - DSST	5D	2 min 2 min	4	CHLORPHENIRAMINE	10	YES	FA
63	Lee et al. (1988)	DSST (WAIS) & Symbol Copying (SCT)	5D	90 sec each	1	CHLORPHENIRAMINE	12	125	N
63	Lee et al. (1988)	MEMORY - STM, words & delay recali	5M	brief	1	CHLORPHENIRAMINE	12		N
59	Khosia et al. (1993)	Card Sorting Task (CST)	5	v brief	1	CHLORPHENIRAMINE	16		N
59	Khosla et al. (1993)	DIGIT SYMBOL Substitution - DSST	5D	v brief	1	CHLORPHENIRAMINE	16		NO
41	Franks et al. (1979)	VERBAL FLUENCY	5	V DINGI	1	CLEMASTINE	1		N
41	Franks et al. (1979)	NUMERICAL REASONING	5		1	CLEMASTINE	1	ļ	' N
91	Peck et al. (1975)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	CLEMASTINE	1	YES	
91	Peck et al. (1975)	MEMORY - STM, 8-digit series x90	5M	15 min	1	CLEMASTINE	1	1	N
97	Reinberg et al. (1978)	Random# ADDITION TEST (P&P)	5	brief	1	CLEMASTINE	1		N
53	Hopes et al. (1992)	Matching Paradigm - Info. Processing	5	10 min?	1	CLEMASTINE	2	YES	
87	Patat et al. (1994)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	CLEMASTINE	2		N
87	Patat et al. (1994)	MEMORY tests - LTM, pictures & delay recall; STM, 15	5M	brief	1	CLEMASTINE	2	1	N
91	Peck et al. (1975)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	CLEMASTINE	2	YES	
91	Peck et al. (1975)	MEMORY - STM, 8-digit series x90	5M	15 min	1	CLEMASTINE	2		f
124	Vuurman et al. (1994)	MEMORY - letters, Sternberg CRT	5M	12 min	1	CLEMASTINE	2	YES	
64	Levander et al. (1985)	TRAIL MAKING - PC-based (~TrailsB)	5T	v. brief	1	CLEMASTINE	3		ł
97	Reinberg et al. (1978)	Random# ADDITION TEST (P&P)	5	brief	1	CLEMASTINE	3	YES	
16	Burns (1990)	VISUAL BACKWARD MASKING -SCRI	5	10+ min	1	DIPHENHYDRAMINE	25		1
17	Burns & Moskowitz (1980)	VISUAL BACKWARD MASKING - SCRI	5	10+ min	1	DIPHENHYDRAMINE	25		I
30	Curran et al. (1998)	WORD RECOGNITION (visual, during ERP)	5	~ 20 min?	1	DIPHENHYDRAMINE	25		1
30	Curran et al. (1998)	DIGIT SYMBOL Substitution - DSST	5D	90 sec	1	DIPHENHYDRAMINE	25		1
30	Curran et al. (1998)	MEMORY - immediate & delayed recall	5M	brief	1	DIPHENHYDRAMINE	25		I
120	Unchern et al. (1986)	Arithmetic (p&p ??)	5	v. brief	1	DIPHENHYDRAMINE	25	YES	
120	Unchern et al. (1986)	Card Sorting Task (4 piles #1-10 each)	5	v. brief	1	DIPHENHYDRAMINE	25		1
120 120	Unchern et al. (1986)	Digit Span ("Recall Memory; F & Backward)	5M	v. brief	1	DIPHENHYDRAMINE	25		
120	Unchern et al. (1986)	Line Test (p&p: draw ~= tracking)	5T	30sec X2	1	DIPHENHYDRAMINE	25	YES	
134	Unchern et al. (1986) Scavone et al. (1998)	T-Maze (p&p: draw ~= tracking)	5T	3 sec	1	DIPHENHYDRAMINE	25	YES	
134	Scavone et al. (1998)	DIGIT SYMBOL Substitution - DSST	5D	?	1	DIPHENHYDRAMINE	25		
31B	Witek, Jr. et al. (1995)	MEMORY - word list, aquisition & recall DIGIT SYMBOL Substitution - DSST	5M	?	1		25		
4	Berlinger et al. (1982)	CARD SORTING TEST B	5D 5	2 min very brief	1		25	YES	
4	Berlinger et al. (1982)	CARD SORTING TEST A	5	very brief	י 1		50	TES	
19	Burns et al. (1994)	VISUAL BACKWARD MASKING - SCRI	5	10+ min	1	DIPHENHYDRAMINE	50 50		
19	Burns et al. (1994)	S-R CONFLICT (SRC) - SCRI	5	~10 min	1	DIPHENHYDRAMINE	50 50	YES	
24	Carruthers et al. (1978)	CARD SORTING tasks	5	v. brief	1	DIPHENHYDRAMINE	50	120	•
30	Curran et al. (1998)	WORD RECOGNITION (visual, during ERP)	5	~ 20 min?	1	DIPHENHYDRAMINE	50		
30	Curran et al. (1998)	DIGIT SYMBOL Substitution - DSST	5D	90 sec	1	DIPHENHYDRAMINE	50		
30	Curran et al. (1998)	MEMORY - immediate & delayed recall	5M	brief	1	DIPHENHYDRAMINE	50		
44	Gengo et al. (1990)	DIGIT SYMBOL Substitution - DSST	5D	90 sec	1	DIPHENHYDRAMINE	50	YES	5
44	Gengo et al. (1990)	Trails B Maze Tracking - p/p test	5T	v. brief	1	DIPHENHYDRAMINE	50	1.20	
56	Katz et al. (1998)	DIGIT SYMBOL Substitution - DSST (WAIS-R)	5D	90 sec	1	DIPHENHYDRAMINE	50		
56	Katz et al. (1998)	MEMORY - Buschke task - word lists	5M	20 min	1	DIPHENHYDRAMINE	50		
56	Katz et al. (1998)	DIGIT SPAN - STM for verbal digits (WAIS-R)	5M	brief	1	DIPHENHYDRAMINE	50	YES	5
56	Katz et al. (1998)	Trails A & B	5T	brief	1	DIPHENHYDRAMINE	50		
57	Kay et al. (1997)	DIGIT SYMBOL Coding - CogScreen	5D	brief	1	DIPHENHYDRAMINE	50		
57	Kay et al. (1997)	WORKING MEMORY - CogScreen	5M	brief	1	DIPHENHYDRAMINE	50	YES	6
66	Lines et al. (1997)	DIGIT SYMBOL Substitution - DSST (~WAIS)	5D	90 sec	1	DIPHENHYDRAMINE	50		
66	Lines et al. (1997)	Verbal MEMORY; immed. & delay recall; PC	5M	brief	1	DIPHENHYDRAMINE	50		
98	Rice & Synder (1993)	Following Directions Test - CCAB	5	v. brief	1	DIPHENHYDRAMINE	50	YES	3
98	Rice & Synder (1993)	Manikan - WRPAB	5	v. brief	1	DIPHENHYDRAMINE	50		
98	Rice & Synder (1993)	Logical Reasoning - WRPAB	5	v. brief	1	DIPHENHYDRAMINE	50		
98	Rice & Synder (1993)	Pattern Comparison - WRPAB	5	v. brief	1	DIPHENHYDRAMINE	50	YES	5
98	Rice & Synder (1993)	Serial ADDITION/SUBTRACTION - WRPAB	5	v. brief	1	DIPHENHYDRAMINE	50	YES	3
98	Rice & Synder (1993)	Interval Production - WRPAB	5	v. brief	1	DIPHENHYDRAMINE	50	1	
98	Rice & Synder (1993)	Time Wall - WRPAB	5	v. brief	1	DIPHENHYDRAMINE	50		
98	Rice & Synder (1993)	Code Substitution - WRPAB	5D	v. brief	1	DIPHENHYDRAMINE	50		
108	Sands et al. (1997)	DIGIT SYMBOL Substitution - DSST (WAIS-R)	5D	90 sec	1	DIPHENHYDRAMINE	50	YES	3
108	Sands et al. (1997)	DIGIT SPAN - STM for verbal digits (WAIS-R)	5M	brief	1	DIPHENHYDRAMINE	50		

108	Sands et al. (1997)	MEMORY - Buschke Task (word lists)	5M	20 min	1	DIPHENHYDRAMINE	50	YES	
108	Sands et al. (1997)	Trails A & B	5T	brief	1	DIPHENHYDRAMINE	50	YES	
116	Spector et al. (1980)	CARD SORTING TESTS (A&B)	5	v. brief	1	DIPHENHYDRAMINE	50		NO
119	Tharion et al. (1994)	Baddeley Grammatical Reasoning (BGRT)	5	3 min	1	DIPHENHYDRAMINE	50		NO
119	Tharion et al. (1994)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	DIPHENHYDRAMINE	50		NO
130A	Witek, Jr. et al. (1992)	Grammatical Reasoning (PC)	5	v. brief	1	DIPHENHYDRAMINE	50		NO
130A	Witek, Jr. et al. (1992)	Arithmetic task (PC)	5	v. brief	1	DIPHENHYDRAMINE	50		NO
130B	Witek, Jr. et al. (1992)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	DIPHENHYDRAMINE	50		NO
131A	Witek, Jr. et al. (1995)	DIGIT SYMBOL Substitution - DSST		2 min	1	DIPHENHYDRAMINE	50		NO
131B	Witek, Jr. et al. (1995)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	DIPHENHYDRAMINE	50		NO
		5	5D	90 sec	1	DIPHENHYDRAMINE	75	YES	
108	Sands et al. (1997)	DIGIT SYMBOL Substitution - DSST (WAIS-R)	5D 5M	8	1	DIPHENHYDRAMINE	75	TEO	NO
108	Sands et al. (1997)	DIGIT SPAN - STM for verbal digits (WAIS-R)		brief 20 min			75	YES	
108	Sands et al. (1997)	MEMORY - Buschke Task (word lists)	5M		. 1	DIPHENHYDRAMINE		YES	
108	Sands et al. (1997)	Trails A & B	5T	brief	1	DIPHENHYDRAMINE	75		
68	Mattila et al. (1986)	DIGIT SYMBOL Substitution - DSST	5D	3 min	1	DIPHENHYDRAMINE	100	YES	
68	Mattila et al. (1986)	DIGIT SPAN (Backward, verbaily)	5M	v. brief	1	DIPHENHYDRAMINE	100	YES	
94	Preston et al. (1992)	DIGIT SYMBOL Substitution - DSST (PC)	5D	v. brief	1	DIPHENHYDRAMINE	100		NO
94	Preston et al. (1992)	MEMORY - Picture Recog/Recall	5M	v. brief	1	DIPHENHYDRAMINE	100		NO
94	Preston et al. (1992)	Enter & Recall Test - Digits (PC)	5M	v. brief	1	DIPHENHYDRAMINE	100	YES	
106	Saarialho-Kere et al. (1989)	DIGIT SYMBOL Substitution - DSST	5D	3 min	1	DIPHENHYDRAMINE	100		NO
94	Preston et al. (1992)	DIGIT SYMBOL Substitution - DSST (PC)	5D	v. brief	1	DIPHENHYDRAMINE	200	YES	1
94	Preston et al. (1992)	MEMORY - Picture Recog/Recall	5M	v. brief	1	DIPHENHYDRAMINE	200	YES	
94	Preston et al. (1992)	Enter & Recall Test - Digits (PC)	5M	v. brief	1	DIPHENHYDRAMINE	200	YES	
64	Levander et al. (1985)	TRAIL MAKING - PC-based (~TrailsB)	5T	v. brief	1	HYDROXYZINE	20		NO
65	Levander et al. (1991)	Perceptual MAZE Test - PC-based	5	v. brief	1	HYDROXYZINE	20		NO
43	Gengo et al. (1987)	Stroop color/word test - PC version	5	brief	1	HYDROXYZINE	25	YES	
9	Blom et al. (1992)	STERNBERG MEMORY & CRT - SRT-C	5M		1	HYDROXYZINE	30	1	NO
21	Bye et al. (1974)	DIGIT SYMBOL Substitution (DSST)	5D	90 sec	1	TRIPOLIDINE	2.5		NO
48	Hamilton et al. (1982)	DIGIT SYMBOL Substitution - DSST	5D	90 sec	1	TRIPOLIDINE	2.5		NO
82	Nicholson & Stone (1986)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	2.5		NO
91	Peck et al. (1975)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	TRIPOLIDINE	2.5	1	NO
91	Peck et al. (1975)	MEMORY - STM, 8-digit series x90	5M	15 min	1	TRIPOLIDINE	2.5		NO
21	Bye et al. (1974)	DIGIT SYMBOL Substitution (DSST)	5D	90 sec	1	TRIPOLIDINE	5	1	NO
22	Bye et al. (1977)	DIGIT SYMBOL Substitution (DSST)	5D	90 sec	1	TRIPOLIDINE	5	YES	
22	Bye et al. (1977)	MEMORY - STM for 8-digit numbers	5M	15 min	1	TRIPOLIDINE	5	YES	
82	Nicholson & Stone (1986)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	5		NO
83	Nicholson et al. (1991)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	5		NO
91	Peck et al. (1975)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	TRIPOLIDINE	5	YES	
91	Peck et al. (1975)	MEMORY - STM, 8-digit series x90	5M	15 min	1	TRIPOLIDINE	5		NO
123	Volkerts et al. (1992)	Letter Matching Task	5	~10 min	1	TRIPOLIDINE	5		NO WP
123	Volkerts et al. (1992)	MEMORY - Digit Scanning (Sternberg)	5M	~13 min	1	TRIPOLIDINE	5	YES	l l
117	Swire et al. (1989)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	TRIPOLIDINE	7.5	YES	
117	Swire et al. (1989)	DIGIT SPAN - STM for verbal digits (WAIS)	5M	v. brief	1	TRIPOLIDINE	7.5		NO
12	Bradley & Nicholson (1986)	DIGIT SYMBOL SUBSTITUTION - DSS	5D	~5 min	1	TRIPOLIDINE	10	1	NO
14	Bradley & Nicholson (1987)	DIGIT SYMBOL SUBSTITUTION - DSS	5D	~5 min	1	TRIPOLIDINE	10	YES	
14	Bradley & Nicholson (1987)	MEMORY - STM - digits visually	5M	8 min	1	TRIPOLIDINE	10	YES	
58	Kerr et al. (1994)	Stroop task - color/word (PC-based)	5	?	1	TRIPOLIDINE	10		NO
58	Kerr et al. (1994)	Sternberg STM - MEMORY, digits visual (PC-based)	5M	v. brief	1	TRIPOLIDINE	10		NO
77	Nicholson & Stone (1982)	ARITHMETIC Test (p&p)	5	10 min	1	TRIPOLIDINE	10		NO
77	Nicholson & Stone (1982)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	10	1	NO
78	Nicholson et al. (1982)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	10		NO
79	Nicholson & Stone (1983)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	10	YES	
80	Nicholson & Stone (1984)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	10	YES	1
82	Nicholson & Stone (1986)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	10	YES	
104	Rombaut et al. (1991)	MEMORY - Word recognition (PC)	5M	v. brief	1	TRIPOLIDINE	10		NO
104	Rombaut et al. (1991)	MEMORY - STM, Sternberg (PC)	5M	v. brief	1	TRIPOLIDINE	10	YES	
13A	Bradley et al. (1987)	DIGIT SYMBOL SUBSTITUTION - DSS	5D	~5 min	1	TRIPOLIDINE	10	YES	
13B	Bradley et al. (1987)	DIGIT SYMBOL SUBSTITUTION - DSS	5D	~5 min	1	TRIPOLIDINE	10	YES	
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34 Discretion et al (1980) CARD SOCTING by etc./ob/vor (Char Dockmon) 5 ord 2 ANTEMUZCLE 10 NO 71 Notacion A Start (1980) ANTEMUZCLE 10 NO 71 Notacion A Start (1980) Control (1980) Control (1980) NO NO 71 Notacion A Start (1980) Control (1980) Notacion A Start (1980) NO NO 71 Notacion A Start (1980) Control (1980) Notacion A Start (1980) Notacion A Start (1980) No 71 Notacion A Start (1980) Notacion (1980) Notacion (1980) Notacion (1980) No 72 Notacion (1980) Notacion (1980) Notacion (1980) No No 73 Notacion (1980) Notacion (1980) No No No No 74 Notacion (1980) No No No No No 75 No No No No No No 75 No No No No No No </th <th></th> <th></th> <th></th> <th></th> <th></th> <th>2nd</th> <th>Generation Drugs:</th> <th>Γ</th> <th></th>						2nd	Generation Drugs:	Γ	
61 Homanu & Easter (1990) Stopp test - control (1) 5 C 2 ATTENUCUE 10 NO 7 Nonzon & Store (1990) DOIT SYNED, Superkare, DSST 50 2 ATTENUCUE 10 NO 8 Res & Synder (1990) DOIT SYNED, Superkare, DSST 50 2 ATTENUCUE 10 NO 98 Res & Synder (1980) Merikan, WRPAB 5 V. bref 2 ATTENUCUE 10 NO 98 Res & Synder (1983) Merikan, WRPAB 5 V. bref 2 ATTENUCUE 10 NO 98 Res & Synder (1983) Sterket ACONTONUERTRACTION V. BYRAB 5 V. bref 2 ATTENUCUE 10 NO 98 Res & Synder (1983) Stestkaton- WRPAB 6 V. bref 2 ATTENUCUE 10 NO 113 Begae & Synder (1980) DOIT SYNED, Substaton, DSST 50 3 3 NO ATTENUCUE 30 NO 113 Begae & Synder (1980) DO	34	Dhorranintra et al. (1986)	CARD SORTING test (CNS problem solving)	5	brief	2	ASTEMIZOLE	10	NO
71 Notakin A Store (1982) ARTMATCH Cat (pkg) 5 10 min 2 ASTEMUCUE 10 NO 71 Notakina A Sine (1982) DAGI SYMEO, Substaturo - DSST 60 2 mm 2 ASTEMUCUE 10 NO 74 Motokina A Sine (1983) DAGI SYMEO, Substaturo - DSST 60 2 mm 2 ASTEMUCUE 10 NO 86 Rok Sine (1983) Internal Postonico - WPAB 5 v. braf 2 ASTEMUCUE 10 NO 87 Rok Sine (1983) Internal Postonico - WPAB 5 v. braf 2 ASTEMUCUE 10 NO 88 Rok Sine (1983) Code Substaturo - DSST 50 V. braf 2 ASTEMUCUE 10 NO 98 Rok Sine (1983) Code Substaturo - DSST 50 No braf 2 ASTEMUCUE 10 NO 98 Rok Sine (1982) ASTEMUCUE 10 NO ASTEMUCUE 10 NO 98 Rok Sine (198) ASTEMUCUE 2									1
70 Norobox nf al (1962) Opfin SYMBOL Substitution - DSST 6D 2 mm 2 ASTEMIZOLE 10 NO 88 Rok & Synder (1983) Mandam - WRPAB 5 V Intel 2 ASTEMIZOLE 10 NO 88 Rok & Synder (1983) Mandam - WRPAB 5 V Intel 2 ASTEMIZOLE 10 NO 98 Rok & Synder (1983) Teal molocular in WRPAB 5 V Intel 2 ASTEMIZOLE 10 NO 98 Rok & Synder (1983) Teal Will WRPAB 5 V Intel 2 ASTEMIZOLE 10 NO 98 Rok & Synder (1983) Teal Will WRPAB 5 V Intel 2 ASTEMIZOLE 10 NO 98 Rok & Synder (1983) Teal Will Statution COST 50 20 Intel 2 ASTEMIZOLE 20 NO 113 Septes & Sonother (1982) DIGIT SYMDOL Statution COST 50 2 mm 2 CETRICINE 5 NO 4 Ander (1980) DIGIT SYMDOL Statution COST 50 2 mm 2 CETRICINE 5					10 min				1
Bit Deck Synder (1985) Ungeal Research 5 V brief 2 ASTERUZOLE 10 NO Bit Rock Synder (1985) Internel Production - WRPAB 5 V brief 2 ASTERUZOLE 10 NO Bit Rock Synder (1983) Internel Production - WRPAB 5 V brief 2 ASTERUZOLE 10 NO Bit Rock Synder (1983) Time Will - WRPAB 5 V brief 2 ASTERUZOLE 10 NO Bit Rock Synder (1983) Time Will - WRPAB 50 V brief 2 ASTERUZOLE 10 NO Bit Rock Synder (1983) DOIT SYNDED, Substitution - NSST 5D D asteruzoLE 30 NO 13 Seppela Solver (1983) DOIT SYNDED, Substitution - OSST 5D Z min 2 ASTERUZOLE 30 NO 13 Seppela Solver (1983) DOIT SYNDED, Substitution - OSST 5D Z min 2 ASTERUZOLE 30 NO 13 Seppela Solver (1980) <td></td> <td>Nicholson & Stone (1982)</td> <td>DIGIT SYMBOL Substitution - DSST</td> <td></td> <td>2 min</td> <td>2</td> <td>ASTEMIZOLE</td> <td></td> <td>NO</td>		Nicholson & Stone (1982)	DIGIT SYMBOL Substitution - DSST		2 min	2	ASTEMIZOLE		NO
Bit Bit Note 4 Streft 2 ASTEWZOLE 10 NO Bit Rosk S, Synder (1985) Howine Policition - WRPAB 5 V brief 2 ASTEWZOLE 10 NO Bit Rosk S, Synder (1985) General ADDTTONUEUTRACTION WRPAB 5 V brief 2 ASTEWZOLE 10 NO Bit Rosk S, Synder (1983) Destinue Tonue Tonue 10 NO NO Bit Rosk S, Synder (1983) Dotter SWBAD, Subattution - NORA 5 V brief 2 ASTEWZOLE 10 NO 113 Begen & Stance (1982) DOLTT SWBAD, Subattution - DSST 50 D min 2 ASTEWZOLE 20 NO 114 Gengo et al. (1980) DDITT SWBAD, Subattution - DSST 50 D min 2 CETRIZINE 5 NO 2 Gengo et al. (1980) Datattation - DSST 50 D min 2 CETRIZINE 5 NO 3 Dome et al. (1980) Datattation - DSST 50 D min 2 CETRIZINE 5 NO 4 Gengo et a									
98 Ros & Synder (1993) Internel Production - WRPAB 5 bref 2 ASTERUZGLE 10 NO 98 Rox & Synder (1993) Teak Morth ACTOLON - WRPAB 5 V. bref 2 ASTERUZGLE 10 NO 98 Rox & Synder (1993) Teak Morth ACTOLON - WRPAB 5 V. bref 2 ASTERUZGLE 10 NO 98 Rox & Synder (1993) Code Substation - WRPAB 50 V. bref 2 ASTERUZGLE 10 NO 99 Rox & Synder (1993) ANTH-METO Teat (56p) 5 10 mn 2 ASTERUZGLE 20 NO 113 Seppets & Sonder (1992) ANTH-METO Teat (56p) 50 2 min 2 CETRUZH 30 NO 44 Morbion A Turrer (1990) DOIT SYMDEJ Substation - DSST 50 2 min 2 CETRUZH 30 NO 45 Done et al. (1980) Automation a concert set pp 5 10 min 2 CETRUZH 50 NO NO 46				-	R				1
Bit Bit S Synder (1993) Selat ADDTIONUSUITACTION NUMPAB 5 buff 2 ASTENUZGLE 10 NO Bit Bit S Synder (1993) Time Wall NRPAB 5 v. brief 2 ASTENUZGLE 10 NO Bit Bit S Synder (1993) Time Wall NRPAB 5 v. brief 2 ASTENUZGLE 10 NO Bit Bit S Synder (1993) Contra Switzlow NRPAB 5 0 2 ASTENUZGLE 10 NO Bit S Synder (1993) Contra Switzlow NRPAB 5 0 NO 2 ASTENUZGLE 20 NO Bit S Synder (1993) Contra Switzlow NRPAB 5 0 NO 2 ASTENUZGLE 20 NO Bit S Synder (1993) Contra Switzlow NRPAB 5 0 NO 2 ASTENUZGLE 20 NO Bit S Synder (1993) Contra Switzlow NRPAB 5 0 NO 2 ASTENUZGLE 20 NO Bit S Synder (1990) Contra Switzlow NRPAB 5 0 NO 3 <td< td=""><td></td><td></td><td></td><td>-</td><td></td><td></td><td></td><td></td><td></td></td<>				-					
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98 Res & Synder (1983) Time Wait - WRPAB 5 V. brief 2. ASTERUZOLE 10 NO 88 Res & Synder (1983) Code Silustitution - WRPAB 50 No ref 2. ASTERUZOLE 10 NO 89 Res & Synder (1983) Code Silustitution - NST 50 Simmin 2. ASTERUZOLE 00 NO 15 Separts & Solumen (1983) DOIGT SYMBOL Substitution - DSST 50 Zimmin 2. ASTERUZOLE 30 NO 15 Separts & Solumen (1980) DOIGT SYMBOL Substitution - DSST 50 Zimmin 2. ASTERUNCLE 5 NO 16 Gengo et al. (1980) DioTT SYMBOL Substitution - DSST 50 Zimmin 2. CETRUNC 6 NO 16 Dorns et al. (1980) Date in the Maxer memory test - pD 5 7 2. CETRUNC 10 NO 16 Gango et al. (1980) Date in the Maxer memory test - pD 5 10 NO NO NO NO NO <td< td=""><td></td><td></td><td>L 11</td><td></td><td>1</td><td></td><td></td><td></td><td>1</td></td<>			L 11		1				1
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130A Witek, Jr. et al. (1992) Arithmetic task (PC) 5 v. brief 2 TERFENADINE 60 NO 130A Witek, Jr. et al. (1992) Grammatical Reasoning (PC) 5 v. brief 2 TERFENADINE 60 NO 131A Witek, Jr. et al. (1995) DIGIT SYMBOL Substitution - DSST 5D 2 min 2 TERFENADINE 60 NO 82 Nicholson & Stone (1986) DIGIT SYMBOL Substitution - DSST 5D 2 min 2 TERFENADINE 120 NO 123 Volkerts et al. (1992) Letter Matching Task 5 ~10 min 2 TERFENADINE 120 NO				H ·	8				4
130A Witek, Jr. et al. (1992) Grammatical Reasoning (PC) 5 v. brief 2 TERFENADINE 60 NO 131A Witek, Jr. et al. (1995) DIGIT SYMBOL Substitution - DSST 5D 2 min 2 TERFENADINE 60 NO 82 Nicholson & Stone (1986) DIGIT SYMBOL Substitution - DSST 5D 2 min 2 TERFENADINE 120 NO 123 Volkerts et al. (1992) Letter Matching Task 5 ~10 min 2 TERFENADINE 120 NO					8				1
131A Witek, Jr. et al. (1995) DIGIT SYMBOL Substitution - DSST 5D 2 min 2 TERFENADINE 60 NO 82 Nicholson & Stone (1986) DIGIT SYMBOL Substitution - DSST 5D 2 min 2 TERFENADINE 60 NO 123 Volkerts et al. (1992) Letter Matching Task 5 ~10 min 2 TERFENADINE 120 NO				- 11	8				
82 Nicholson & Stone (1986) DIGIT SYMBOL Substitution - DSST 5D 2 min 2 TERFENADINE 120 NO 123 Volkerts et al. (1992) Letter Matching Task 5 ~10 min 2 TERFENADINE 120 NO				H	N				
123 Volkerts et al. (1992) Letter Matching Task 5 ~10 min 2 TERFENADINE 120 NO				11	8				1
		Volkerts et al. (1992)		8	R I				1
	123	Volkerts et al. (1992)	MEMORY - Digit Scanning (Stemberg)	5M	 ∼13 min	2	TERFENADINE	120	NO

MALAN REFERENCE

Page 2: sorted by Generation, DRUG, Dose, Ref#, SC#

TABLE 10.

IMPAIRMENT?

SC# Duration | Gen | DRUG Dose: mg YES | NO

1st Generation Drugs:

					1st	Generation Drugs:			
132	Yasuda et al. (1998)	DIVIDED ATTENTION (PC)	6	v brief	1	CHLORPHENIRAMINE	2	YES	
132	Yasuda et al. (1998)	DIVIDED ATTENTION (PC)	6	v brief	1	CHLORPHENIRAMINE	4	YES	
131B	Witek, Jr. et al. (1995)	DIVIDED ATTENTION (PC)	6	v, brief	1	CHLORPHENIRAMINE	4	120	NO
42	Gaillard et al. (1988)	TRACKING + Continuous Memory Task	6	7 min	1	CLEMASTINE	1	YES	
42	Gaillard et al. (1988)	Continuous MEMORY TASK during Tracking	6	7 min	1	CLEMASTINE	1		NO
124	Vuurman et al. (1994)	DIVIDED ATTENTION - ~SCRI	6	12 min	1	CLEMASTINE	2	YES	
16	Burns (1990)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	25		NO
17	Burns & Moskowitz (1980)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	25	YES	
131B	Witek, Jr. et al. (1995)	DIVIDED ATTENTION (PC)	6	v. brief	1	DIPHENHYDRAMINE	25	YES	
18A	Burns & Moskowitz (1993)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	25		NO?
18B	Burns & Moskowitz (1993)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	25	YES	
19	Burns et al. (1994)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	50	YES	
20	Burns et al. (1999 - ms)	DIVIDED ATTENTION - SCRI ('96 ver)	6	12 min	1	DIPHENHYDRAMINE	50		NO
57 .	Kay et al. (1997)	DIVIDED ATTENTION - CogScreen	6	brief	1	DIPHENHYDRAMINE	50	YES	
73	Moskowitz & Burns (1988)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	50	YES	
102	Roehrs et al. (1993)	DIVIDED ATTENTION - Trk & periph/center targets	6	15 min	1	DIPHENHYDRAMINE	50	YES	·
127	Wilkinson & Moskowitz (1990)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	50	YES	j
129	Wilkinson et al. (1999 - ms)	DIVIDED ATTENTION - SCRI ('96ver)	6	12 min	1	DIPHENHYDRAMINE	50	YES	
130B	Witek, Jr. et al. (1992)		6	v. brief	1	DIPHENHYDRAMINE	50	YES	
131A 131B	Witek, Jr. et al. (1995)	DIVIDED ATTENTION (PC)	6	v. brief	1	DIPHENHYDRAMINE	50	YES	
70	Witek, Jr. et al. (1995) Mobe et el. (1978)		6	v. brief	1	DIPHENHYDRAMINE	50	YES	
106	Mohs et al. (1978) Saarialho-Kere et al. (1989)	DIVIDED ATTENTION (digit transf & itr detect; not PC TRACKING & CRT test (this is D-A!)	6	15 min	1	DIPHENHYDRAMINE DIPHENHYDRAMINE	100 100	YES	NO
111	Seidel et al. (1987)	D-A ("VIG": Trk & periph vs ctr targets)	6	30 min	1	HYDROXYZINE	25	YES	
55	Irving & Jones (1992)	DIVIDED ATTENTION - per SCRI	6	12 min	1	TRIPOLIDINE	25	TES	NO
55	Irving & Jones (1992)	DIVIDED ATTENTION - per SCRI	6	12 min	1	TRIPOLIDINE	2.5 5		NO
121	Valk et al. (1997)	VigTrack - "dual-task" (palmtop PC)	6	5 min	1	TRIPOLIDINE	5	YES	NO
58	Kerr et al. (1994)	TRACKING with D-A task	6	1 min	1	TRIPOLIDINE	10	YES	
104	Rombaut et al. (1991)	DIVIDED ATTENTION - Trk & peripheral signals	6	1 min	1	TRIPOLIDINE	10	120	NO
			-						
					2nd	Generation Drugs:			
51	Hindmarch & Easton (1986)	TRACKING & Peripheral Signals Task	6	1 min	2	ASTEMIZOLE	10		NO
111	Seidel et al. (1987)	D-A ("VIG": Trk & periph vs ctr targets)	6	30 min	2	CETIRIZINE	5		NO
95	Ramaekers et al. (1992)	DIVIDED ATTENTION - per SCRI	6	12 min	2	CETIRIZINE	10	YES	
100	Riedel et al. (1990)	DIVIDED ATTENTION	6		2	CETIRIZINE	10		NO
111	Seidel et al. (1987)	D-A ("VIG": Trk & periph vs ctr targets)	6	30 min	2	CETIRIZINE	10		NO
100	Riedel et al. (1990)	DIVIDED ATTENTION	6		2	CETIRIZINE	20		NO
111	Seidel et al. (1987)	D-A ("VIG": Trk & periph vs ctr targets)	6	30 min	2	CETIRIZINE	20		NO
42	Gaillard et al. (1988)	TRACKING + Continuous Memory Task	6	7 min	2	LORATADINE	10		NO
42	Gaillard et al. (1988)	Continuous MEMORY TASK during Tracking	6	7 min	2	LORATADINE	10	YES	
57 95	Kay et al. (1997)	DIVIDED ATTENTION - CogScreen	6	brief	2	LORATADINE	10		NO bP
95 121	Ramaekers et al. (1992)	DIVIDED ATTENTION - per SCRI	6	12 min	2	LORATADINE	10		NO
127	Valk et al. (1997) Wilkinson & Moskowitz (1990)	VigTrack - "dual-task" (palmtop PC)	6	5 min	2	LORATADINE	10		NO
133	Corner et al. (1998)	DIVIDED ATTENTION - SCR	6	12 min 10 min	2 2	LORATADINE	10		NO
133	Comer et al. (1998)	DIVIDED ATTENTION - Miller et al '88	6	10 min	2	LORATADINE LORATADINE	10 20		NO
42	Gaillard et al. (1988)	Continuous MEMORY TASK during Tracking	6	7 min	2	TERFENADINE	20 60	YES	NO
42	Gaillard et al. (1988)	TRACKING + Continuous Memory Task	6	7 min	2	TERFENADINE	60 60	TEO	NO
58	Kerr et al. (1994)	TRACKING with D-A task	6		2	TERFENADINE	60	}	NO
73	Moskowitz & Burns (1988)	DIVIDED ATTENTION - SCRI	6	12 min	2	TERFENADINE	60		NO 6P
131A	Witek, Jr. et al. (1995)	DIVIDED ATTENTION (PC)	6	v. brief	2	TERFENADINE	60	1	NO
18A	Burns & Moskowitz (1993)	DIVIDED ATTENTION - SCRI	6	12 min	2	TERFENADINE	60		NO
18B	Burns & Moskowitz (1993)	DIVIDED ATTENTION - SCRI	6	12 min	2	TERFENADINE	60		NO
18B	Burns & Moskowitz (1993)	DIVIDED ATTENTION - SCRI	6	12 min	2	TERFENADINE	120	1	NO
			-						

Note: NO bP = NO significant impairment, and performance was better than Placebo. PC = Task presented on computerized system

Sheet: VIG TABLE 11 . VIGILANCE TASKS - Summary of Impairment findings as a function of DRUG and Dose - ACUTE DOSING only

page 2: sorted by Generation, DRUG, Dose, Ref#, SC#

Ref#	REFERENCE	TASK	167-2	Duration	5 (C	DRUG			IRMENT
				Signification (State		DRUG	Dosexmp	MES.	NO
					1st	Generation Drugs:			
91	Peck et al. (1975)	VIGILANCE - Auditory (Wilkinson RT; 1hr)	7	1 hr	1	CLEMASTINE	1	YES	
91	Peck et al. (1975)	VIGILANCE - Auditory (Wilkinson RT; 1hr)	7	h hr	1	CLEMASTINE	2	YES	
124	Vuurman et al. (1994)	VIGILANCE - Sustained Attention, Vis.	7?	11 min	1	CLEMASTINE	2	1.50	NO
122	Vermeeren et al. (1998)	VIGILANCE - Sustained Attention - ~ SCRI (45min)	7	45 min	1	CLEMASTINE	3		NO wP
16	Burns (1990)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	25	YES	NO WP
38	Fine et al. (1994)	VIGILANCE - Visual, 2-hr (10min blks x12)	7	2 hr	1	DIPHENHYDRAMINE	25	YES	
18A	Burns & Moskowitz (1993)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	25	YES	
18B	Burns & Moskowitz (1993)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	25	YES	
19	Burns et al. (1994)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	25 50	YES	
20	Burns et al. (1999 - ms)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	50 50		
39	Fink et al. (1979)	Continuous Perf Task (CPT) during EEG	7		1	DIPHENHYDRAMINE		YES	
56	Katz et al. (1998)	Continuous Performance Task (vig?)	7	brief	1		50	YES	
57	Kay et al. (1997)	Continuous Perf. Task - Kay G	7	5 min	1	DIPHENHYDRAMINE	50	YES	
66	Lines et al. (1997)	VIGILANCE - Sustained Attention, Vis.	7	10 min	1	DIPHENHYDRAMINE	50	YES	
66	Lines et al. (1997)	VIGILANCE - Sustained Attention, Aud.	7	$\sim 10 \text{ min} \times 2$	•	DIPHENHYDRAMINE	50	YES	
73	Moskowitz & Burns (1988)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	50		NO
108	Sands et al. (1997)	Continuous Performance Task (vig?)	7	brief	1	DIPHENHYDRAMINE	50	YES	
110	Schweitzer et al. (1994)	Simulated Assembly Line Task - SALT (PC)	7	1 hr	1	DIPHENHYDRAMINE	50	YES	
126	Walsh et al. (1994)	Simulated Assembly Line Task - SALT (PC)	7	1 hr x4	-	DIPHENHYDRAMINE	50	YES	
127	Wilkinson & Moskowitz (1990)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	50	YES	
129	Wilkinson et al. (1999 - ms)	VIGILANCE - SCRI	7	40 min 40 min	1	DIPHENHYDRAMINE	50	YES	
108	Sands et al. (1997)	Continuous Performance Task (vig?)	7	40 min brief	1	DIPHENHYDRAMINE	50	YES	
68	Mattila et al. (1986)	ATTENTION Test (concentrated attn?)	77	8	1	DIPHENHYDRAMINE	75	YES	
125	Walsh et al. (1992)	Simulated Assembly Line Task - SALT (PC)	1 .	5 min	1	DIPHENHYDRAMINE	100		NO wB
21	Bye et al. (1974)	VIGILANCE - Auditory	7	50 min x8	1	HYDROXYZINE	25	YES	
91	Peck et al. (1975)	VIGILANCE - Auditory (Wilkinson RT; 1hr)	7	1 hr	1	TRIPOLIDINE	2.5	YES	
21	Bye et al. (1974)	VIGILANCE - Auditory (Whitemson RT; Thr)	7	1 hr	1	TRIPOLIDINE	2.5	YES	
22	Bye et al. (1977)	VIGILANCE - Auditory	7	1 hr	1	TRIPOLIDINE	5	YES	
91	Peck et al. (1975)		7	1 hr	1	TRIPOLIDINE	5	YES	
•		VIGILANCE - Auditory (Wilkinson RT; 1hr)	7	1 hr	1	TRIPOLIDINE	5	YES	
					2nd	Generation Drugs:			
84	Nicholson et al. (1998)	VIGILANCE - Visual digits, 15min	7	15 min	2	CETIRIZINE	5		20
84	Nicholson et al. (1998)	VIGILANCE - Visual digits, 15min	7	15 min	2	CETIRIZINE	10		NO
100	Riedel et al. (1990)	VIGILANCE	7		2	CETIRIZINE	-		NO
110	Schweitzer et al. (1994)	Simulated Assembly Line Task - SALT (PC)	7	1 hr	2	CETIRIZINE	10		NO
125	Walsh et al. (1992)	Simulated Assembly Line Task - SALT (PC)	7	50 min x8	2		10		NO
126	Walsh et al. (1994)	Simulated Assembly Line Task - SALT (PC)	7	1 hr x4	2	CETIRIZINE	10		NO?1>
84	Nicholson et al. (1998)	VIGILANCE - Visual digits, 15min	7	15 min	2	CETIRIZINE	10		NO
100	Riedel et al. (1990)	VIGILANCE	7		2	CETIRIZINE	20	1	NO
122	Vermeeren et al. (1998)	VIGILANCE - Sustained Attention - ~ SCRI (45min)	7	45 min	2	CETIRIZINE	20		NO
122	Vermeeren et al. (1998)	VIGILANCE - Sustained Attention - ~`SCRI (45min)	7	45 min	2	FEXOFENADINE	120	1	NO
57	Kay et al. (1997)	Continuous Perf. Task - Kay G	7		_	FEXOFENADINE	240		NO
127	Wilkinson & Moskowitz (1990)	VIGILANCE - SCRI	7	5 min	2	LORATADINE	10		NO
39	Fink et al. (1979)	Continuous Perf Task (CPT) during EEG	7	40 min	2	LORATADINE	10		NO
73	Moskowitz & Burns (1988)	VIGILANCE - SCRI	7		2	TERFENADINE	60		NO
18A	Burns & Moskowitz (1993)	VIGILANCE - SCRI		40 min	2	TERFENADINE	60		NO bP
	Burns & Moskowitz (1993)	VIGILANCE - SCRI	7	40 min.	2	TERFENADINE	60	1	NO
18B									
18B 18B	Burns & Moskowitz (1993)	VIGILANCE - SCRI	7	40 min 40 min	2 2	TERFENADINE	60 120	1	NO

Note: NO wP = NO significant impairment, but worse than Placebo.

NO wB = NO significant impairment, but worse than Baseline.

NO bP = NO significant impairment, and better than Placebo.

NO? 1x = only one measure at single time point, of many, was significantly impaired. PC = Task presented on computerized system. RT = Reaction Time

TRACKING TASKS - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only

sheet: TRACK SC# 8, 8Cr

TABLE 12.

	Page 2: sorted by Generation, D							IMPAIR	
Refi	REFERENCE	TASK (or Subjective SEDATION)	1	Duration	Gen	DRUG	Dose: mg	YES	HO
					1st	Generation Drugs:			
26	Clarke & Nicholson (1978)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	CHLORPHENIRAMINE	4	YES	
61	Kulshrestha et al. (1978)	PURSUIT ROTOR - (Tracking)	8	brief	1	CHLORPHENIRAMINE	4		NO
76	Nicholson (1979)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	CHLORPHENIRAMINE	4		NC
26	Clarke & Nicholson (1978)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	CLEMASTINE	1	YES	
42	Gaillard et al. (1988)	TRACKING - Pursuit; performed alone	8	7 min	1	CLEMASTINE	1	YES	
93	Pishkin et al. (1983)	PURSUIT ROTOR - (Tracking)	8	v. brief	1	CLEMASTINE	1		N
112	Seppala et al. (1981)	TRACKING Task (steer black dot on trk)	8	30 sec	1	CLEMASTINE	1		NC
53	Hopes et al. (1992)	TRACKING - Rotor & Pursuit tasks	8	10 min ea?	1	CLEMASTINE	2	YES	
93	Pishkin et al. (1983)	PURSUIT ROTOR - (Tracking)	8	v. brief	1	CLEMASTINE	2		N
124	Vuurman et al. (1994)	CRITICAL TRACKING (CTT) - ~SCRI (5 trials)		5 min	1	CLEMASTINE	2	YES	
64	Levander et al. (1985)	TRACKING, Adaptive (~VMC per Nicholson)		8 min	1	CLEMASTINE	3	YES	
122	Vermeeren et al. (1998)	CRITICAL TRACKING (CTT) - ~SCRI (5 trials			1	CLEMASTINE	3	YES	
16	Burns (1990)	CRITICAL TRACKING (CTT) - SCRI		20+ min	1	DIPHENHYDRAMINE	25	YES	
17	Burns & Moskowitz (1980)	COMPENSATORY TRACKING - SCRI	8	6 min	1	DIPHENHYDRAMINE	25	1.50	N
17	Burns & Moskowitz (1980)	CRITICAL TRACKING (CTT) - SCRI	-	20+ min	1	DIPHENHYDRAMINE	25		NO
27	Cohen et al. (1984)	TRACKING - Adaptive (VMC)		10 min	1	DIPHENHYDRAMINE	25	YES	110
67	Linnoila (1973)	TRACKING (Coordination tests & II)	8	v. brief	1	DIPHENHYDRAMINE	25	120	N
18A	Burns & Moskowitz (1993)	CRITICAL TRACKING (CTT) - SCRI		20+ min	1	DIPHENHYDRAMINE	25	YES	1.0
18B	Burns & Moskowitz (1993)	CRITICAL TRACKING (CTT) - SCRI		20+ min	1	DIPHENHYDRAMINE	25	YES	
20	Burns et al. (1999 - ms)	CRITICAL TRACKING (CTT) - SCRI	1	20+ min	1	DIPHENHYDRAMINE	23 50	163	NO
27	Cohen et al. (1984)	TRACKING - Adaptive (VMC)	H	10 min	1	DIPHENHYDRAMINE	50	YES	NO
29	Cohen et al. (1987)	TRACKING - Adaptive (VMC)	a	10 min	1	DIPHENHYDRAMINE	50	YES	
29 57	Kay et al. (1997)	TRACKING - solo via CogScreen	8	brief	1	DIPHENHYDRAMINE	50	YES	
67	Linnoila (1973)	TRACKING (Coordination tests & II)	8	v, brief	1	DIPHENHYDRAMINE	50	TES	N
73	Moskowitz & Burns (1988)	CRITICAL TRACKING (CTT) - SCRI	a -		1	DIPHENHYDRAMINE	50	YES	
93	Pishkin et al. (1983)	PURSUIT ROTOR - (Tracking)	8	v. brief	1		50	TES	
98	Rice & Snyder (1993)		9 -		1	DIPHENHYDRAMINE		YES	N
127	Wilkinson & Moskowitz (1990)	TRACKING - WRPAB (Unstable Trking) CRITICAL TRACKING (CTT) - SCRI	8	v. brief 20+ min	1	DIPHENHYDRAMINE	50		
129	Wilkinson et al. (1999 - ms)	3	8Cr		1	DIPHENHYDRAMINE	50	YES	
130A	Witek, Jr. et al. (1999 - ms)	CRITICAL TRACKING (CTT) - SCRI TRACKING	8Cr		-	DIPHENHYDRAMINE	50	YES	
27		TRACKING - Adaptive (VMC)	8	v. brief	1	DIPHENHYDRAMINE	50	YES	
68	Cohen et al. (1984)		8Cr		1	DIPHENHYDRAMINE	100	YES	
64	Mattila et al. (1986)	TRACKING Task (Coordination test)	8	30 sec	1	DIPHENHYDRAMINE	100		NO
93	Levander et al. (1985) Pishkin et al. (1983)	TRACKING, Adaptive (~VMC per Nicholson)	8Cr	8 min	1	HYDROXYZINE	20	YES	
93 28	Cohen et al. (1985)	PURSUIT ROTOR - (Tracking)	8	v. brief	1	HYDROXYZINE	25	VE	N
20 55	Irving & Jones (1992)	TRACKING - Adaptive (VMC)	H	10 min	1	TRIPOLIDINE	2.5	YES	
55 76	Nicholson (1979)	Adaptive TRACKING - Pursuit (Critical?)	8	10 min	1	TRIPOLIDINE	2.5	-	N
28	Cohen et al. (1985)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	u · • · · · · · ·	1	TRIPOLIDINE	2.5	YES	
∠≎ 55	Irving & Jones (1992)	TRACKING - Adaptive (VMC)		10 min	1	TRIPOLIDINE	5	YES	
12	• • •	Adaptive TRACKING - Pursuit (Critical?)	8	10 min	1	TRIPOLIDINE	5		N
14	Bradley & Nicholson (1986)	TRACKING (Vis. Motor Coord. = VMC)	8Cr		1	TRIPOLIDINE	10	YES	
76	Bradley & Nicholson (1987)	TRACKING (Vis. Motor Coord. = VMC)		10 min	1	TRIPOLIDINE	10	YES	
76	Nicholson (1979)	TRACKING (Vis. Motor Coord. = VMC)		10 min	1	TRIPOLIDINE	10	YES	
	Nicholson & Stone (1982)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	14	1	TRIPOLIDINE	10	YES	
79	Nicholson & Stone (1983)	TRACKING (Vis. Motor Coord. = VMC)	8	10 min	1	TRIPOLIDINE	10	YES	
80	Nicholson & Stone (1984)	TRACKING (Vis. Motor Coord. = VMC)	8Cr		1	TRIPOLIDINE	10	YES	
82	Nicholson & Stone (1986)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	12	1	TRIPOLIDINE	10	YES	
13A	Bradley et al. (1987)	TRACKING (Vis. Motor Coord. = VMC)	8Cr		1	TRIPOLIDINE	10	YES	
13B	Bradley et al. (1987)	TRACKING (Vis. Motor Coord. = VMC)	BCr	10 min	1	TRIPOLIDINE	10	YES	

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sheet: TRACK SC# 8, 8Cr

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continued... Page 2: sorted by Generation, DRUG, Dose, Ref#, SC#.

	a heren en se	TASK (or Subjective SEDATION)		<u>Ouralieus</u>		DRGG	S SERVICE SERVICE		
					2nd	Generation Drugs:			
77	Nicholson & Stone (1982)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	ASTEMIZOLE	20		NC
113	Seppala & Savolainen (1982)	TRACKING - "Coord Task ("steer black dot on	8	30 sec	2	ASTEMIZOLE	30		N
84	Nicholson & Turner (1998)	TRACKING Task (compensatory?)	8	3 min	2	CETIRIZINE	5	YES	
84	Nicholson & Turner (1998)	TRACKING Task (compensatory?)	8	3 min	2	CETIRIZINE	10		N
95	Ramaekers et al. (1992)	CRITICAL TRACKING (CTT) - ~SCRI, but 5tri	8Cr	brief	2	CETIRIZINE	10		N
100	Riedel et al. (1990)	CRITICAL TRACKING (CTT)	8Cr		2	CETIRIZINE	10	YES	
84	Nicholson & Turner (1998)	TRACKING Task (compensatory?)	8	3 min	2	CETIRIZINE	20	YES	
100	Riedel et al. (1990)	CRITICAL TRACKING (CTT)	8Cr		2	CETIRIZINE	20	YES	
122	Vermeeren et al. (1998)	CRITICAL TRACKING (CTT) - ~SCRI (5 trials	8Cr	v. brief	2	FEXOFENADINE	120	YES	
122	Vermeeren et al. (1998)	CRITICAL TRACKING (CTT) - ~SCRI (5 trials			2	FEXOFENADINE	240	YES	
14	Bradley & Nicholson (1987)	TRACKING (Vis. Motor Coord. = VMC)		10 min	2	LORATADINE	10		N
42	Gaillard et al. (1988)	TRACKING - Pursuit; performed alone	8	7 min	2	LORATADINE	10		N
57	Kay et al. (1997)	TRACKING - solo via CogScreen	8	brief	2	LORATADINE	10		N
95	Ramaekers et al. (1992)	CRITICAL TRACKING (CTT) - ~SCRI, but 5tri	8Cr	brief	2	LORATADINE	10		N
127	Wilkinson & Moskowitz (1990)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	2	LORATADINE	10		N
14	Bradley & Nicholson (1987)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	LORATADINE	20		N
14	Bradley & Nicholson (1987)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	LORATADINE	40		N
26	Clarke & Nicholson (1978)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	TERFENADINE	60		N
42	Gaillard et al. (1988)	TRACKING - Pursuit; performed alone	8	7 min	2	TERFENADINE	60		N
61	Kulshrestha et al. (1978)	PURSUIT ROTOR - (Tracking)	8	brief	2	TERFENADINE	60		N
73	Moskowitz & Burns (1988)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	2	TERFENADINE	60	1	NC
77	Nicholson & Stone (1982)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	TERFENADINE	60		N
79	Nicholson & Stone (1983)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	TERFENADINE	60		N
82	Nicholson & Stone (1986)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	TERFENADINE	60	1	N
130A	Witek, Jr. et al. (1992)	TRACKING	8	v. brief	2	TERFENADINE	60		N
18A	Burns & Moskowitz (1993)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	2	TERFENADINE	60		. N
18B	Burns & Moskowitz (1993)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	2	TERFENADINE	60		N
82	Nicholson & Stone (1986)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	TERFENADINE	120		٨
18B	Burns & Moskowitz (1993)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	2	TERFENADINE	120	1	N

NOTE: Across all types of TRACKING TASKS, the 1st generation drugs were found to be significantly impairing in 68.8% of the times tested; this is compared to 18.8% for the 2nd generation drugs. However, when CRITICAL TRACKING TASKS specifically were used, impairment was found in 90.3% (28/31) vs 19.0% (4/21) of the cases, for the 1st and 2nd generation drugs, respectively. Moreover, at least 2 of the 3 test findings for the 1st generation drugs which were not significant nonetheless showed performance which was clearly worse than Placebo ("NO wP" in table above) and in fact approached statistical significance (p < 0.08).

-9

i

Sheet: RT Tasks TABLE 13. REACTION TIME TASKS - Summary of Impairment findings as a function of DRUG and Dose - ACUTE DOSING only

SC# 9 Page 2: sorted by Generation, DRUG, Dose, Ref#, SC#.

Bish (1979) COMPLEX REACTION TEST SC			TASK	8. e. s	Carculon	Gen	DRUG	Constant States	IMPAIR	
6 Behr (1775) REACTION TIME - simple '' 53 53 Durd 1 CLOPAPHEWIRKANNE 4 YES 6 Dimanna tet al (1974) REACTION TIME - Conjece (dig)t) 35 C <										
6 Behr (1775) REACTION TIME - simple '' 53 53 Durd 1 CLOPAPHEWIRKANNE 4 YES 6 Dimanna tet al (1974) REACTION TIME - Conjece (dig)t) 35 C <	8	Right (1070)								
35 Devramming et al. (1990) REACTION TIME - consigned (ptr) SC Deal 1 Decomplexity (ptr) Parks et al. (1977) REACTION TIME - complexity (ptr) SS Deal NO 131 Pranks et al. (1977) REACTION TIME - Simple (ptr) SS Deal TO HLOPRHEIRRANNE 4 NO 131 Wink JL et al. (1980) REACTION TIME - Complex (ptr) SS Deal TO HLOPRHEIRRANNE 1 VLOR NO 131 Wink JL et al. (1983) REACTION TIME - Complex (ptr) SC V. Def TO LLOPRHEIRRANNE 1 VLOR NO 14 Frains et al. (1977) REACTION TIME - Simple (afgle (ptr) SS SS To LLOPANTIME 1 NO 15 Parkin et al. (1983) REACTION TIME - Simple (ST), Aud 2 Via SS SS SS SS SS No NO 16 CLEMASTINE 1 CLEMASTINE 1 NO NO 17 Sepatas et al. (1983) REACTION TIME - Simple (ST), Aud 2 Via SS SS SS SS		. ,			5					
40 Franks et al. (1979) REACTON TIME: Complex 5C 1 C+CORPHENIXAMINE 4 NO 67 Kulthrefhe et al. (1976) REACTON TIME: Simple (unit) 55 brief 1 C+CORPHENIXAMINE 4 NO 151 Wink, Lin (1976) REACTON TIME: Simple (unit) 55 brief 1 C+CORPHENIXAMINE 4 NO 151 Wink, Lin (1976) REACTON TIME: Simple (Unit) SS brief 1 C+CORPHENIXAMINE 1 VISB NO 162 Gelland et al. (1975) REACTON TIME: Simple (UNIT), Aud SS 1 C-EMASTINE 1 NO 17 Gelland et al. (1983) REACTON TIME; Simple (UNIT), Aud SS 1 C-MINT 1 C-EMASTINE 1 NO 17 Septiale at (1984) REACTON TIME; Simple (UNIT), Aud SS 1 Mint 1 C-MINT NO 17 Septiale at (1984) REACTON TIME; Choid (USIT), Vauit SC Dime 1 C-MINT NO 18				8					VEC	NO
40 Franks et al. (1978) FRACTION TIME - Simple (gripp) 95 Soft 1 C-ALCORPHENTRAMINE 4 NO 1316 Witek, ir. et al. (1986) REACTION TIME - Simple (gripp) 95 Vitek 1 C-ALCORPHENTRAMINE 4 YES 1316 Witek, ir. et al. (1986) REACTION TIME - Simple, studied vite (gripp) 95 Vitek 1 C-BLARSTINE 1 NO 141 Franks et al. (1975) REACTION TIME - Simple, studied vite (gripp) 95 1 C-BLARSTINE 1 NO 142 Grippe at al. (1975) REACTION TIME - Simple, studied vite (gripp) 95 1 C-BLARSTINE 1 NO 142 Separate et al. (1987) REACTION TIME - Simple, vite (gripp) 95 1 C-BLARSTINE 1 NO 142 Separate et al. (1987) REACTION TIME - Chock (STT), Visual 9 5 1 C-BLARSTINE 1 NO 142 Separate et al. (1987) REACTION TIME - Chock (STT), Visual 9 5 1 C-BLARSTINE 2 YES 142 Versement et al. (1986) REACTION TIME - Chock (STT), Visual				A .	Driei				TEO	NO
61 Kubinesthe et al. (1972) FEACTON TIME - Simple (angle ign) 95 braff 1 CURCEPTENTRAMINE 4 YES 151 Wirks, X. et al. (1992) REACTON TIME, SIMPLE - Auditory S5 Vol CRPHENTRAMINE 1 YES 163 Lee et al. (1983) REACTON TIME, SIMPLE - Auditory S5 Vol CLEMASTINE 1 NO 163 Lee et al. (1987) REACTON TIME, SIMPLE - Auditory S5 1 CLEMASTINE 1 NO 163 Parking et al. (1987) REACTON TIME, SIMPLE - Auditory S5 1 CLEMASTINE 1 NO 164 Parking et al. (1987) REACTON TIME, SIMPLE - Auditory S5 0 1 CLEMASTINE 1 NO 167 Parking et al. (1987) REACTON TIME, SIMPLE Additory, Aud S5 5 0 1 NO 168 Lewonder et al. (1987) REACTON TIME, Choice (CRT), Vaul S5 5 0 1 1 ND 164 Lewonder et al. (1986) REACTON TIME, Choice (CRT), Vaul S5	40			11						1
1316 Witek, <i>ir. et al.</i> (1998) REACTION TIME, Choice (CRT), Vis CO. Visef 1 1 YES 41 Franks et al. (1979) REACTION TIME - Complex. SC. Visef 1 CLICRPHENTAMINE 1 NO 42 Galilard et al. (1989) REACTION TIME - Simple Aud A Vis SS Visef 1 CLICRPHENTAMINE 1 NO 43 Previse et al. (1973) REACTION TIME - Simple AUX Aud SS Visef 1 CLEMASTINE 1 NO 44 Previse et al. (1975) REACTION TIME, Simple SKT, Aud SS 1 NO 1 NO 47 Previse et al. (1985) REACTION TIME, Simple SKT, Aud SS 1 No 1 NO 41 Levender et al. (1985) REACTION TIME, Simple SKT, Aud SS 1 No 1 No 42 Levender et al. (1986) REACTION TIME, Choice (CXT), Vis (L&R v. distration) SS No No 1 No 43 Levender et al. (1986) REACTION TIME, Choice (CXT), Vis	61	Kulshrestha et al. (1978)		11	brief					1
63 Lee et al. (1989) REACTION TIME, SIMPLE - Auditory B5 V. Ind ²	131B	Witek, Jr. et al. (1995)		11					YES	
41 Franke et al. (1979) REACTION TIME - Complex. 9C 1 CLEMASTINE 1 NO 42 Gallad et al. (1987) REACTION TASK - visual fletic cipia, dogradod 9S 24 min 1 CLEMASTINE 1 NO 42 Gallad et al. (1987) REACTION TASK - visual fletic cipia, dogradod 9S 24 min 1 CLEMASTINE 1 NO 43 Parking et al. (1987) REACTION TIME, SINTE (SCR), dogradod fletifierence Task), or inter inter cipital statistics 2 YEB 44 Levender et al. (1985) REACTION TIME, SINTE (Scr), visual 00 Finital inter cipital statistics 2 YEB NO 44 Levender et al. (1985) REACTION TIME, Choose (XFU), visual 05 No ref 1 CLEMASTINE 3 YEB NO 45 Levender et al. (1985) REACTION TIME, Choose (XFU), visual 9S No ref 1 CLEMASTINE 3 YEB NO 122 Vermerrer et al. (1986) REACTION TIME, Choose (CRT), visual 9S No ref 1 CLEMASTINE <t< td=""><td>63</td><td>Lee et al. (1988)</td><td>REACTION TIME, SIMPLE - Auditory</td><td>95</td><td>v. brief</td><td></td><td></td><td></td><td></td><td></td></t<>	63	Lee et al. (1988)	REACTION TIME, SIMPLE - Auditory	95	v. brief					
41 Franks et al. (1973) REACTION TIME - Simple, Aud & Vis. 95	41	Franks et al. (1979)		90						NO
42 Gallard et al (1985) REACTION TASK - runal field: digite, digate,	41	Franks et al. (1979)	REACTION TIME - Simple, Aud & Vis	95		1	CLEMASTINE	1		1
93 Planktin et al. (1993) REACTION TIME_STR 2 GRT (Speedod Interference Task); 0 V bord 1 CLEMASTINE 1 NO 12 Septidie et al. (1993) REACTION TIME_ Choole (CRT); Visual 9C 50 train 1 CLEMASTINE 2 YES 13 Perket et al. (1993) REACTION TIME_ Choole (CRT); Visual 9C V brief 1 CLEMASTINE 2 YES 14 Lewarder et al. (1993) REACTION TIME_ Choice (CRT); Visual 9C V brief 1 CLEMASTINE 3 YES 14 Lewarder et al. (1993) REACTION TIME_ Choice (CRT); Visual 9S V brief 1 CLEMASTINE 3 YES 15 Lewarder et al. (1993) REACTION TIME_ Choice (CRT); Visual 9S V brief 1 DIPHEN+TORAINE 25 YES 13 Visiter 10194 REACTION TIME_ Choice (CRT); Visual 9S V brief DIPHEN+TORAINE 25 YES 14 Certen et al. (1973) REACTION TIME - Single; Visual 9S V brief DIPHEN+TORAI	42	Gaillard et al. (1988)	REACTION TASK - visual field: digits, degraded	9	24 min	1	CLEMASTINE	1		1
112 Sepplate at J (1991) Complex CFT, (winus), pesification) oc mm 1 CEMASTINE 1 MO 97 Petet et J (1994) REACTION TIME, Shipping (RT), Yuluul SS 15 min 1 CEMASTINE 2 YES 91 Pelohie at J (1985) REACTION TIME, STR (STR (Speeded Interferone Task); 9 Voline 1 CLEMASTINE 2 YES 124 Levander et al (1986) REACTION TIME, Single (RT), Yuluul 9C Voline 1 CLEMASTINE 3 YES 122 Vermeren et al (1984) REACTION TIME, Chole (CRT), Yie (LR w distraction) 9C Voline 1 DIPHENHYDRAININE 25 YES 121 Were, et al (1982) REACTION TIME, Chole (CRT), Vie all 9C Voline 1 DIPHENHYDRAININE 25 YES NO 121 Wirek, et al (1980) REACTION TIME, Single (Visual 9S Voline 1 DIPHENHYDRAININE 50 NO 121 Wirek et al (1997) REACTION TIME, Single (Visual 9S Simin<1					15 min	1	CLEMASTINE	1	YES	
87 Perint et al. (1984) Perint et al. (1987) REACTION TIME, Single (REIN), Judu Soc. Soc. Soc. Soc. Soc. Soc. Soc. Soc.		· ·	REACTION TIME, SRT & CRT (Speeded Interference Task);	9	v. brief	1	CLEMASTINE	1		NO
91 Peck et al. (1975) REACTION TIME. Simple (RTI), Aug. 95 95 75 76				90	~1min	1	CLEMASTINE	1		NO
93 Piehlin et al. (1983) REACTION TIME. SPIT & CRT (Speeded Interference Task); 0 w brief 1 CLEMASTINE 2 No 64 Levander et al. (1986) REACTION TIME - Chock visual 0 w brief 1 CLEMASTINE 3 YEB 72 Verseener al. (1984) REACTION TIME, Chock (CRT); Vis (LR.w. distractors) 0 w brief 1 CLEMASTINE 3 YEB 71 Cohen et al. (1984) REACTION TIME, Chock (CRT); Vis (LR.w. distractors) 0 v brief 1 DIPHENNYDRAMINE 25 YEB 71 Linnole (1973) REACTION TIME - Simple, Visual 9C v brief 1 DIPHENNYDRAMINE 50 NO 71 Cohen et al. (1987) REACTION TIME - Simple, Visual 9S 5 min 1 DIPHENNYDRAMINE 50 YEB 7 Cohen et al. (1987) REACTION TIME - Simple, Visual 9S 5 brief 1 DIPHENNYDRAMINE 50 NO 7 Cohen et al. (1987) REACTION TIME, Simple (GAPSTINE 9S brief 1 DIPHENNYDRAMINE 50 NO				8	50 trials	1	CLEMASTINE	2	YES	
64 Levander et al (1986) REACTION TIME - Conce, visual 70 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 8 <					15 min	1	CLEMASTINE	2	YES	
64 Levander et al. (1986) REACTION TIME - Simple, aud. Sviugal 65 r. brain 1 OLEMASTINE 3 YES 72 Cohen et al. (1984) REACTION TIME - Choice (CRT), Vis. (L&R.w. detractors) 65 r. brain 1 DEPEENHYDRAMINE 25 YES NO 73 Cohen et al. (1984) REACTION TIME - Choice (CRT), Vis. 65 r. brain 1 DEPEENHYDRAMINE 25 YES NO 74 Deringer et al. (1982) REACTION TIME - Simple, Visual 95 v. brief 1 DEPEENHYDRAMINE 50 YES NO 74 Cohen et al. (1987) REACTION TIME - Simple, Visual 95 v. brief 1 DEPEENHYDRAMINE 50 YES NO 75 Kay et al. (1997) REACTION TIME - Simple, Visual 95 brief 1 DEPEENHYDRAMINE 50 YES NO 76 Linoble (177.3) REACTION TIME - Simple, Visual 95 brief 1 DEPEENHYDRAMINE 50 NO 78 Readment et al. (1987) REACTION TIME - Simple, Visual 95 brief 1 DEPEENHYDRAMINE				R -	8					NO
112 Vermeener et al. (1999) REACTION TIME. Choise (CRT); Vise (LBR w. distractors) 3C Visiter al. (1904) 3 NO 27 Cohen et al. (1996) REACTION TIME. Simple, Visual 3C Visiter al. (1904) 3 Visiter al. (1904) YES NO 1318 Witek, Jr. et al. (1994) REACTION TIME. Choise (CRT); Vis. 3C Visiter al. (1904) YES NO 24 Cambre et al. (1994) REACTION TIME - Simple, Visual SS Visiter al. (1904) YES NO 25 Cohen et al. (1994) REACTION TIME - Simple, Visual SS Smin 1 DIPHEENHYDRANINE 50 YES 26 Cohen et al. (1997) REACTION TIME - Simple, Visual SS Smin 1 DIPHEENHYDRANINE 50 YES 27 Kay et al. (1997) REACTION TIME - Simple, Visual SS Smin 1 DIPHEENHYDRANINE 50 NO 28 Kay et al. (1997) REACTION TIME - Simple, CogSoreen SS brief 1 DIPHEENHYDRANINE 50 NO 29				12	8					
27 Cohen et al. (1994) REACTION TIME - Simple Visual Sond 10 DH-ED-NYDERAININE 25 VISI NO 1318 Witek, Jr. et al. (1995) REACTION TIME - Choice (CRT) So. vinif DIPHED-NYDERAININE 25 VISI NO 24 Berlingert al. (1995) REACTION TIME - Simple So. vinif DIPHED-NYDERAININE 50 VISI NO 24 Carnuthers et al. (1976) REACTION TIME - Simple Visual 55 vinif DIPHED-NYDERAININE 50 YES NO 24 Cohen et al. (1987) REACTION TIME - Simple Visual 55 sinif DIPHED-NYDERAININE 50 YES NO 56 Katz et al. (1986) REACTION TIME - Simple: Visual 55 sinif DIPHED-NYDERAININE 50 YES NO 57 Kay et al. (1987) REACTION TIME - Simple: Visual 55 sinif DIPHED-NYDERAININE 50 YES NO 58 Innoia (1733) REACTION TIME - Simple: Visual 55 No NO <t< td=""><td></td><td>• •</td><td></td><td>6</td><td></td><td></td><td></td><td></td><td>YES</td><td></td></t<>		• •		6					YES	
67 Linola (1973) REACTION TIME, Choice (CSTT), Via CC V. Torier 1 DIPHENHYDRAMINE 25 VIEs NO 4138 Wirks, J. et al. (1982) REACTION TIME, Choice (CSTT), Via SC V. Drief DIPHENHYDRAMINE SS NO 42 Cambra et al. (1983) REACTION TIME - simple, Visual SS K. Diref DIPHENHYDRAMINE SO VIEs NO 22 Cohen et al. (1987) REACTION TIME - Simple, Visual SS Smin DIPHENHYDRAMINE SO VIEs NO 23 Cohen et al. (1987) REACTION TIME - Simple, Visual SS Smin DIPHENHYDRAMINE SO VIEs 54 Kaiz et al. (1987) REACTION TIME, Simple, Xuala SS Forial DIPHENHYDRAMINE SO NO 56 Linnoia (1873) REACTION TIME, Simple, Kaiza SC No Inf DIPHENHYDRAMINE SO NO 57 Kaiz et al. (1983) REACTION TIME, Simple, Kaiza SC Visit DIPHENHYDRAMINE SO NO 58				li i	-					NO
1318 Wiek, Jr et al. (1995) REACTION TIME. Choice (CRT), Vie 00 View Diref DIPHEDN/YDRAMINE 25 VIE 4 Beringer et al. (1995) REACTION TIME - simple, Visual 35 Vibref DIPHEDN/YDRAMINE 50 NO 24 Caruthere et al. (1994) REACTION TIME - simple, Visual 35 5 min DIPHEDN/YDRAMINE 50 YES 27 Cohen et al. (1997) REACTION TIME - Simple, Visual 35 5 min DIPHEDN/YDRAMINE 50 YES 28 Cohen et al. (1997) REACTION TIME - Simple, Visual 35 5 min DIPHEDN/YDRAMINE 50 NO 56 Katz et al. (1997) REACTION TIME, Choice (&CPR1) 35 5 min DIPHEDN/YDRAMINE 50 NO 51 Korder (1993) Four Choice (&CPR1) 35 brief DIPHEDN/YDRAMINE 50 NO 53 Cohen et al. (1997) REACTION TIME, VRPA (1994) 9 forief DIPHEDN/YDRAMINE 50 NO 54 Sandse tal. (1997) REACTION TIME, Choice (CRT), Vis		• •		N					YES	
4 Beringer et al. (1982) REACTION TIME - Simple, visual 55 Very Diref 1 DIPHENH-YDRAMINE 50 YES 24 Caruthers et al. (1976) REACTION TIME - Simple, visual 95 Simin 1 DIPHENH-YDRAMINE 50 YES 27 Cohen et al. (1987) REACTION TIME - Simple, visual 95 Simin 1 DIPHENH-YDRAMINE 50 YES 28 Cohen et al. (1997) REACTION TIME - Simple, visual 95 Simin 1 DIPHENH-YDRAMINE 50 NO 61 Lines et al. (1997) REACTION TIME, Choice (&CRT) 95 brief 1 DIPHENH-YDRAMINE 50 NO 7 Linnolit (1973) REACTION TIME, Simple (SRT) 90 v. brief 1 DIPHENH-YDRAMINE 50 NO 108 Sande et al. (1983) REACTION TIME, Simple (SRT) - visual 9 v. brief 1 DIPHENH-YDRAMINE 50 NO 108 Sande et al. (1982) REACTION TIME, Single (SRT) - visual 95 v. brief 1 DIPHENH-YD		· ·			*				VEC	NO
24 Carrulhers al. (1976) REACTION TIME - simple, visual 35 V. brief 1 DIPHENH/YDRAMINE 50 YES 27 Cohen et al. (1987) REACTION TIME - Simple, Visual 95 5 mm 1 DIPHENH/YDRAMINE 50 YES 29 Cohen et al. (1987) REACTION TIME - Simple, Visual 95 5 mm 1 DIPHENH/YDRAMINE 50 YES 56 Katz et al. (1997) REACTION TIME - Simple, Visual 95 5 Find 1 DIPHENH/YDRAMINE 50 NO 61 Lines et al. (1997) REACTION TIME - Simple, Visual 95 5 Find 1 DIPHENH/YDRAMINE 50 NO 63 Lines et al. (1997) REACTION TIME - Simple, Visual 95 visidef 1 DIPHENH/YDRAMINE 50 NO 64 Lines et al. (1992) REACTION TIME - Simple (SRT) - visual 95 visidef 1 DIPHENH/YDRAMINE 50 NO 7030 Wrek, Jr. et al. (1992) REACTION TIME - Choice (CRT), Vis 96<				11	-				TES	
27 Cohene et al. (1984) REACTION TIME - Simple, Vaual 95 Simin 1 DIPHENHYDRAMINE 50 YES 29 Cohene et al. (1997) REACTION TIME - Simple, Vaual 95 Simin 1 DIPHENHYDRAMINE 50 YES 57 Kay et al. (1997) REACTION TIME - Simple, Cogiscreen 95 Diref 1 DIPHENHYDRAMINE 50 NO 61 Lines et al. (1997) REACTION TIME, Cogiscreen 95 Diref 1 DIPHENHYDRAMINE 50 NO 62 Lines et al. (1997) REACTION TIME, Choice (CRT) 90 Diref 1 DIPHENHYDRAMINE 50 NO 97 Risk det al. (1993) REACTION TIME, Simple (Speeded Interference Task); 9 V. brief 1 DIPHENHYDRAMINE 50 NO 108 Sands et al. (1993) REACTION TIME, Simple (Speeded Interference Task); 9 V. brief 1 DIPHENHYDRAMINE 50 NO 108 Sands et al. (1992) REACTION TIME, Choice (CRT), Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 1308 Wrek, Jr. et al. (1992) REACTION TIME, Choice (CRT), Vis 9C V. brief 1 DIPHENHY					8				VEe	
2 Cohene et al. (1987) REACTION TIME - Simple, Yaual 95 Smin 1 DIPHENHYDRAMINE 50 YES 56 Katz et al. (1987) REACTION TIME - Simple, Yaual? 95 brief 1 DIPHENHYDRAMINE 50 YES 76 Lines et al. (1997) REACTION TIME, Choice (ACPRT) 95 brief 1 DIPHENHYDRAMINE 50 NO 66 Lines et al. (1987) REACTION TIME, Choice (ACRT) 96 brief 1 DIPHENHYDRAMINE 50 NO 71 Inoile (1573) REACTION TIME, Choice (ACRT) Vert 1 DIPHENHYDRAMINE 50 NO 73 Pierkin et al. (1980) REACTION TIME, Choice (ACRT), Visual 95 vief 1 DIPHENHYDRAMINE 50 YES 730A Wate, Jr. et al. (1982) REACTION TIME, Choice (CRT), Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 731A Wate, Jr. et al. (1982) REACTION TIME, Choice (CRT), Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES		· · ·		11					1	
56 Katz et al. (1999) REACTION TIME - Simple (ogscreen ogscreen	29			1					1	
57 Kay et al. (1997) REACTION TIME - Simple; CogSoreen 95 brief 1 DIPHENH-YDRAMINE 50 NO 66 Lineola (1973) REACTION TIME, Choleg (& CPRT) 9C brief 1 DIPHENH-YDRAMINE 50 NO 97 Pishkin et al. (1983) REACTION TIME, Choleg (& CPRT) 9C brief 1 DIPHENH-YDRAMINE 50 NO 98 Rice & Snyder (1983) REACTION TIME, Choleg (& CPRT) 9C V. brief 1 DIPHENH-YDRAMINE 50 NO 108 Sands et al. (1987) REACTION TIME, CNR (NRPAB 9C V. brief 1 DIPHENH-YDRAMINE 50 NO 1303 Witek, Jr. et al. (1992) REACTION TIME, Choleg (CRT), Vis 9C V. brief 1 DIPHENH-YDRAMINE 50 YES 1314 Witek, Jr. et al. (1992) REACTION TIME, Choleg (CRT), Vis 9C V. brief 1 DIPHENH-YDRAMINE 50 YES 1318 Witek, Jr. et al. (1984) REACTION TIME, Choleg (CRT), Vis 9C V. brief 1 <	56	Katz et al. (1998)								
66 Lines et al. (1997) REACTION TIME, Choice (A CPRT) 9C orief 1 DIPHENHYDRAMINE 50 NO 67 Linnoile (1973) REACTION TIME, Choice (CRT) 9C v. brief 1 DIPHENHYDRAMINE 50 NO 98 Rice & Singder (1993) Four Choice REACTION TIME - WRPAB 9C v. brief 1 DIPHENHYDRAMINE 50 NO 108 Sands et al. (1997) REACTION TIME - (PC task) 9 brief 1 DIPHENHYDRAMINE 50 NO 1304 Wrtek, Jr. et al. (1992) REACTION TIME, Choice (CRT); Vis 9S v. brief 1 DIPHENHYDRAMINE 50 YES 1318 Wrtek, Jr. et al. (1995) REACTION TIME, Choice (CRT); Vis 9C v. brief 1 DIPHENHYDRAMINE 50 YES 1318 Wrtek, Jr. et al. (1995) REACTION TIME, Choice (CRT); Vis 9C v. brief 1 DIPHENHYDRAMINE 50 YES 1318 Wrtek, Jr. et al. (1996) REACTION TIME, Choice (CRT); Vis & 40 9C v. brief 1 DIPHENHYDRAMINE 50 YES 1318 Wrtek, Jr	57	Kay et al. (1997)		12	1					NO
67 Linnolie (1973) REACTION TIME, Choice (CRT) 9C v. brief 1 DIPHENHYDRAMINE 50 NO 93 Pieblin et al (1983) REACTION TIME, SRT & CRT (Speedel Interference Task); 9 v. brief 1 DIPHENHYDRAMINE 50 NO 98 Rice & Snyder (1993) Four Choice REACTION TIME - WRPAB 9 brief 1 DIPHENHYDRAMINE 50 NO 108 Sands et al (1997) REACTION TIME, Simple (SRT) - visual 9 v. brief 1 DIPHENHYDRAMINE 50 YES 1300 Wrtek, Jr. et al (1992) REACTION TIME, Choice (CRT); Vis 9C v. brief 1 DIPHENHYDRAMINE 50 YES 1318 Wrtek, Jr. et al (1995) REACTION TIME, Choice (CRT); Vis 9C v. brief 1 DIPHENHYDRAMINE 50 YES 1318 Wrtek, Jr. et al (1984) REACTION TIME, Choice (CRT); Vis & Aud 9C v. brief 1 DIPHENHYDRAMINE 50 YES 1318 Wrtek, Jr. et al (1984) REACTION TIME (choice (CRT); Vis & Aud 9C	66	Lines et al. (1997)		90					1	
93 Pishkin et al. (1983) REACTION TIME, SRT & CRT (Speeded Interference Task); 9 v. brief 1 DIPHENH+TORAMINE 50 NO 108 Sands et al. (1997) REACTION TIME - (PC task) 9 brief 1 DIPHENH+TORAMINE 50 NO 116 Spector et al. (1980) REACTION TIME - (PC task) 9 brief 1 DIPHENH+TORAMINE 50 NO 130A Witek, Jr et al. (1982) REACTION TIME; Choice (CRT); Vis 9C v. brief 1 DIPHENH+TORAMINE 50 YES 130A Witek, Jr et al. (1985) REACTION TIME; Choice (CRT); Vis 9C v. brief 1 DIPHENH+TORAMINE 50 YES 131B Witek, Jr et al. (1985) REACTION TIME; Choice (CRT); Vis 9C v. brief DIPHENH-TORAMINE 50 YES 131B Witek, Jr et al. (1985) REACTION TIME; Choice (CRT); Vis 9C v. brief DIPHENH-TORAMINE 50 YES 131B Witek, Jr et al. (1984) REACTION TIME; Choice (CRT); Vis & Aud 9C v. brief DIPHENH-T		Linnoila (1973)	REACTION TIME, Choice (CRT)	90	v. brief					1
108 Sands et al. (1997) REACTION TIME (PC task) 30 bit if 1 DiPLENHYDRAMINE 50 YES 116 Spector et al. (1980) REACTION TIME (C) task) 35 v. brief 1 DIPLENHYDRAMINE 50 YES 130A Witek, Jr. et al. (1992) REACTION TIME, Choice (CRT), Vis 9C v. brief 1 DIPLENHYDRAMINE 50 YES 130A Witek, Jr. et al. (1992) REACTION TIME, Choice (CRT), Vis 9C v. brief 1 DIPLENHYDRAMINE 50 YES 131B Witek, Jr. et al. (1995) REACTION TIME, Choice (CRT), Vis 9C v. brief 1 DIPLENHYDRAMINE 50 YES 131B Witek, Jr. et al. (1984) REACTION TIME, Choice (CRT), Vis 9C v. brief 1 DIPHENHYDRAMINE 75 YES 108 Mattilia et al. (1986) REACTION TIME, Choice (CRT), Vis & Aud 9C v. brief 1 DIPHENHYDRAMINE 100 YES 108 Mattilia et al. (1984) REACTION TIME + STR & CRT 9 v. brief 1 DIPHENHYDRAMINE 100 NO 94		. ,	REACTION TIME, SRT & CRT (Speeded Interference Task);	9	v. brief	1	DIPHENHYDRAMINE	50		
116 Spector et al. (1980) REACTION TIME, Simple (SRT) - visual 95 V. brief 1 DIPHENHYDRAMINE 50 NO 130A Witek, Jr. et al. (1992) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 131A Witek, Jr. et al. (1992) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 131B Witek, Jr. et al. (1995) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 131B Witek, Jr. et al. (1995) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 1308 Standa et al. (1997) REACTION TIME, Choice (CRT); Vis & Aud 9C V. brief 1 DIPHENHYDRAMINE 100 NO 94 Preston et al. (1992) REACTION TIME Choice (CRT); Vis & Aud 9C V. brief 1 DIPHENHYDRAMINE 100 NO 94 Preston et al. (1982) REACTION TIME Choice; Visual 9C				90	v. brief	1	DIPHENHYDRAMINE	50		NO
130A Witek, Jr. et al. (1992) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 130B Witek, Jr. et al. (1992) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 131B Witek, Jr. et al. (1995) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 131B Witek, Jr. et al. (1995) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 130B Witek, Jr. et al. (1995) REACTION TIME (Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 70 YES 130B Mattila et al. (1986) REACTION TIME (Choice (CRT); Vis & Aud 9C V. brief 1 DIPHENHYDRAMINE 100 NO 140 Preston et al. (1982) REACTION TIME (Choice (CRT); Vis & Aud 9C V. brief 1 DIPHENHYDRAMINE 200 NO 14 Preston et al. (1982) REACTION TIME (Choice (CRT); Vis & Aud <td< td=""><td></td><td></td><td></td><td>9</td><td>brief</td><td>1</td><td>DIPHENHYDRAMINE</td><td>50</td><td>YES</td><td></td></td<>				9	brief	1	DIPHENHYDRAMINE	50	YES	
130B Witek, Jr. et al. (1992) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 131A Witek, Jr. et al. (1995) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 131B Witek, Jr. et al. (1995) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 131B Witek, Jr. et al. (1995) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 130B Sands et al. (1997) REACTION TIME, Choice (CRT); Vis & Aud 9C V. brief 1 DIPHENHYDRAMINE 100 YES 140B REACTION TIME, Choice (CRT); Vis & Aud 9C V. brief 1 DIPHENHYDRAMINE 100 NO 94 Preston et al. (1992) REACTION TIME tests - SRT & CRT 9 V. brief 1 DIPHENHYDRAMINE 100 NO 94 Preston et al. (1985) REACTION TIME - Simple; aud & visual 9C V. brief 1 HYDROXYZINE 20 NO 95 Levander e					li li			50		NO
131A Witek, Jr. et al. (1995) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 131B Witek, Jr. et al. (1995) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 131B Witek, Jr. et al. (1995) REACTION TIME, Choice (CRT); Vis 9C V. brief 1 DIPHENHYDRAMINE 50 YES 131B Sands et al. (1997) REACTION TIME, Choice (CRT); Vis & Aud 9S brief 1 DIPHENHYDRAMINE 100 YES 27 Cohen et al. (1984) REACTION TIME, Choice (CRT); Vis & Aud 9C v. brief 1 DIPHENHYDRAMINE 100 NO 94 Preston et al. (1992) REACTION TIME Estes - SRT & CRT 9 v. brief 1 DIPHENHYDRAMINE 200 NO 94 Preston et al. (1992) REACTION TIME - Choice; visual 9C v. brief 1 DIPHENHYDRAMINE 200 NO 94 Levander et al. (1985) REACTION TIME - Choice; visual 9C v. brief 1 HYDROXYZINE 20 YES 95		. ,		8	H				1	
131B Witek, Jr. et al. (1995) REACTION TIME, Choice (CRT); Vis 05 V. brief 1. DIPHENH/DRAMINE 50 YES 108 Sands et al. (1987) REACTION TIME, Choice (CRT); Vis 9 brief 1. DIPHENH/DRAMINE 50 YES 27 Cohen et al. (1984) REACTION TIME, Choice (CRT); Vis & Aud 9C v. brief 1. DIPHENH/DRAMINE 100 YES 86 Mattila et al. (1986) REACTION TIME, Choice (CRT); Vis & Aud 9C v. brief 1. DIPHENH/DRAMINE 100 NO 94 Preston et al. (1992) REACTION TIME tests - SRT & CRT 9 v. brief 1. DIPHENH/DRAMINE 00 NO 94 Preston et al. (1992) REACTION TIME tests - SRT & CRT 9 v. brief 1. DIPHENH/DRAMINE 20 NO 94 Preston et al. (1985) REACTION TIME - Choice; visual 9C v. brief 1. DIPHENH/DRAMINE 20 NO 94 Levander et al. (1985) REACTION TIME - Simple; aud & visual 9C v. brief 1. HYDROXYZINE 20 NO 95 Levander et al. (1985) REACTION TIME, Simple; aud & visual 9C v. brief				1					1	
108 Sands et al. (1997) REACTION TIME - (PC task) 9 bitch 1 DIPHENHYDRAMINE 75 YES 27 Cohen et al. (1984) REACTION TIME - Simple, Visual 9S 5 min 1 DIPHENHYDRAMINE 100 NO 94 Preston et al. (1992) REACTION TIME choice (CRT); Vis & Aud 9C V. brief 1 DIPHENHYDRAMINE 100 NO 94 Preston et al. (1992) REACTION TIME tests - SRT & CRT 9 V. brief 1 DIPHENHYDRAMINE 200 NO 94 Preston et al. (1992) REACTION TIME tests - SRT & CRT 9 V. brief 1 DIPHENHYDRAMINE 200 NO 94 Preston et al. (1992) REACTION TIME - Choice; visual 9C V. brief 1 HYDROXYZINE 20 YES 64 Levander et al. (1991) REACTION TIME - Simple; aud & visual 9S V. brief 1 HYDROXYZINE 20 NO 93 Pishkin et al. (1983) REACTION TIME - Simple, Auditory 9S 5min<1				11	fi					
27Cohen et al. (1984)REACTION TIME - Simple, Visual95S min1DIPHENHYDRAMINE100YES68Mattila et al. (1986)REACTION TIME, Choice (CRT); Vis & Aud9CV. brief1DIPHENHYDRAMINE100NO94Preston et al. (1992)REACTION TIME tests - SRT & CRT9V. brief1DIPHENHYDRAMINE100NO94Preston et al. (1982)REACTION TIME tests - SRT & CRT9V. brief1DIPHENHYDRAMINE200NO64Levander et al. (1985)REACTION TIME - Choice; visual9CV. brief1HYDROXYZINE20YES64Levander et al. (1985)REACTION TIME - Choice; visual9CV. brief1HYDROXYZINE20NO65Levander et al. (1985)REACTION TIME - Choice; visual9CV. brief1HYDROXYZINE20NO65Levander et al. (1985)REACTION TIME - Choice; visual9CV. brief1HYDROXYZINE20NO66Levander et al. (1983)REACTION TIME - Simple; aud & visual9CV. brief1HYDROXYZINE20NO72Brack (1985)REACTION TIME - Simple; Nisual9S15 min1TRIPOLIDINE2.5NO73Pishtin et al. (1983)REACTION TIME - Simple, Visual9S15 min1TRIPOLIDINE2.5NO74Peck et al. (1975)REACTION TIME - Simple, Nisual9S15 min1TRIPOLIDINE5YES									1	
68Mattile et al. (1986)REACTION TIME, Choice (CRT), Vis & Aud9CV. brief1DIPIELNITIONAMINE100NO94Preston et al. (1992)REACTION TIME tests - SRT & CRT9V. brief1DIPIENHYDRAMINE100NO94Preston et al. (1992)REACTION TIME tests - SRT & CRT9V. brief1DIPIENHYDRAMINE200NO94Preston et al. (1985)REACTION TIME tests - SRT & CRT9V. brief1DIPIENHYDRAMINE200NO94Levander et al. (1985)REACTION TIME - Choice; visual9CV. brief1HYDROXYZINE20YES95Levander et al. (1985)REACTION TIME - Simple; aud & visual9CV. brief1HYDROXYZINE20NO95Levander et al. (1991)REACTION TIME, SImple; aud & visual9SV. brief1HYDROXYZINE20NO96Levander et al. (1991)REACTION TIME, SIT & CRT (Speeded Interference Task);9V. brief1HYDROXYZINE20NO97Peck et al. (1982)REACTION TIME, Simple, Kaud955min1TRIPOLIDINE2.5YES98Peck et al. (1975)REACTION TIME - Auditory915min1TRIPOLIDINE5YES98Cohen et al. (1985)REACTION TIME, Simple (SRT), Aud955min1TRIPOLIDINE5YES91Peck et al. (1977)REACTION TIME, Simple (SRT), Aud955m				H					1	
94Preston et al. (1992)REACTION TIME tests - SRT & CRT9v. brief1DIPHENHYDRAMINE100NO94Preston et al. (1992)REACTION TIME tests - SRT & CRT9v. brief1DIPHENHYDRAMINE200NO64Levander et al. (1985)REACTION TIME - Choice; visual9Cv. brief1HYDROXYZINE20YES64Levander et al. (1985)REACTION TIME - Choice; visual9Cv. brief1HYDROXYZINE20YES65Levander et al. (1991)REACTION TIME - Simple; aud & visual9Cv. brief1HYDROXYZINE20NO65Levander et al. (1991)REACTION TIME - Simple; aud & visual9Cv. brief1HYDROXYZINE20NO93Pishkin et al. (1983)REACTION TIME - Simple; aud & visual9Sv. brief1HYDROXYZINE20NO84Hamilton et al. (1985)REACTION TIME - Simple, Visual9S5min1TRIPOLIDINE2.5YES28Cohen et al. (1975)REACTION TIME - Simple, Auditory9S15 min1TRIPOLIDINE2.5YES28Cohen et al. (1985)REACTION TIME - Simple, Visual9S5min1TRIPOLIDINE5YES29Peck et al. (1977)REACTION TIME - Simple, Visual9S15 min1TRIPOLIDINE5YES28Cohen et al. (1985)REACTION TIME - Simple, Visual9S5 min1TRIPOLIDINE <t< td=""><td>68</td><td>· · ·</td><td></td><td>8</td><td>8</td><td></td><td></td><td></td><td>160</td><td>NO</td></t<>	68	· · ·		8	8				160	NO
94Preston et al. (1992)REACTION TIME tests - SRT & CRT9v. brief1DIPHENHYDRAMINE200NO64Levander et al. (1985)REACTION TIME - Choice; visual9Cv. brief1HYDROXYZINE20YES64Levander et al. (1985)REACTION TIME - Choice; visual9Sv. brief1HYDROXYZINE20YES65Levander et al. (1991)REACTION TIME - Choice; visual9Sv. brief1HYDROXYZINE20NO65Levander et al. (1991)REACTION TIME - Simple; aud & visual9Sv. brief1HYDROXYZINE20NO65Levander et al. (1983)REACTION TIME - Simple; aud & visual9Sv. brief1HYDROXYZINE20NO93Pishkin et al. (1983)REACTION TIME, SRT & CRT (Speeded Interference Task);9v. brief1HYDROXYZINE20NO28Cohen et al. (1985)REACTION TIME - Simple, Visual9S15 min1TRIPOLIDINE2.5YES29Peck et al. (1975)REACTION TIME - Simple (SRT); Aud9S15 min1TRIPOLIDINE5YES28Cohen et al. (1985)REACTION TIME, Simple (SRT); Aud9S5 min1TRIPOLIDINE5YES217Swire et al. (1987)REACTION TIME, Simple (SRT), 4ud9S15 min1TRIPOLIDINE5YES29Peck et al. (1987)REACTION TIME, Simple (SRT), 4ud9S5min1TRIPOLIDINE	94	Preston et al. (1992)	REACTION TIME tests - SRT & CRT	R	8					
64Levander et al. (1985)REACTION TIME - Choice; visual9Cv. brief1HYDROXYZINE20YES64Levander et al. (1985)REACTION TIME - Simple; aud & visual9Sv. brief1HYDROXYZINE20YES65Levander et al. (1991)REACTION TIME - Choice; visual9Cv. brief1HYDROXYZINE20NO65Levander et al. (1991)REACTION TIME - Choice; visual9Cv. brief1HYDROXYZINE20NO93Pishkin et al. (1983)REACTION TIME - Simple; aud & visual9Sv. brief1HYDROXYZINE26NO28Cohen et al. (1985)REACTION TIME - Simple, Visual9Sv. brief1HYDROXYZINE25NO28Cohen et al. (1982)REACTION TIME - Simple, Visual9S5min1TRIPOLIDINE2.5YES20By et al. (1975)REACTION TIME - Simple, Auditory9S15min1TRIPOLIDINE2.5YES22By et al. (1975)REACTION TIME - Simple, Visual9S15min1TRIPOLIDINE5YES24Cohen et al. (1985)REACTION TIME - Simple, Visual9S5min1TRIPOLIDINE5YES25By et al. (1977)REACTION TIME - Simple, Visual9S5min1TRIPOLIDINE5YES25NoREACTION TIME - Simple, Visual9S5min1TRIPOLIDINE5YES <td>94</td> <td>Preston et al. (1992)</td> <td></td> <td>10 -</td> <td>1</td> <td></td> <td></td> <td></td> <td></td> <td></td>	94	Preston et al. (1992)		10 -	1					
65Levander et al. (1991)REACTION TIME - Choice; visual9Cv. brief1HYDROXYZINE20NO65Levander et al. (1991)REACTION TIME - Simple; aud & visual9Sv. brief1HYDROXYZINE20NO93Pishkin et al. (1983)REACTION TIME, SRT & CRT (Speeded Interference Task);9v. brief1HYDROXYZINE26NO28Cohen et al. (1985)REACTION TIME, SRT & CRT (Speeded Interference Task);9v. brief1HYDROXYZINE25NO28Cohen et al. (1985)REACTION TIME, Simple, Visual9S5 min1TRIPOLIDINE2.5YES29Peck et al. (1975)REACTION TIME, Simple (SRT); Aud9S15 min1TRIPOLIDINE2.5YES28Cohen et al. (1985)REACTION TIME - Simple, Visual9S5 min1TRIPOLIDINE5YES28Cohen et al. (1975)REACTION TIME, Simple (SRT); Aud9S5 min1TRIPOLIDINE5YES29Peck et al. (1975)REACTION TIME, Simple (SRT) - during ERP9S8 min1TRIPOLIDINE7.5NO117Swire et al. (1986)REACTION TIME - Choice (CRT) Leads9C-5 min1TRIPOLIDINE10NO12Bradley & Nicholson (1986)REACTION TIME - ComPLEX - CRT9C-5 min1TRIPOLIDINE10NO13ABradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1TRIPOLIDIN	64	Levander et al. (1985)	REACTION TIME - Choice; visual	90					YES	
65Levander et al. (1991)REACTION TIME - Simple; aud & visual9SV. brief1HYDROXYZINE20NO93Pishkin et al. (1983)REACTION TIME, SRT & CRT (Speeded Interference Task);9v. brief1HYDROXYZINE25NO28Cohen et al. (1985)REACTION TIME - Simple, Visual9S5min1TRIPOLIDINE2.5YES48Hamilton et al. (1982)REACTION TIME - Simple, Auditory9S15min1TRIPOLIDINE2.5YES91Peck et al. (1975)REACTION TIME - Simple, (SRT); Aud9S15min1TRIPOLIDINE2.5YES22Bye et al. (1975)REACTION TIME - Simple, Visual9S5min1TRIPOLIDINE5YES28Cohen et al. (1985)REACTION TIME - Simple, Visual9S5min1TRIPOLIDINE5YES29Peck et al. (1975)REACTION TIME - Simple, Visual9S5min1TRIPOLIDINE5YES91Peck et al. (1985)REACTION TIME, Simple (SRT), Aud9S15min1TRIPOLIDINE5YES117Swire et al. (1986)REACTION TIME, Simple (SRT) - during ERP9S8min1TRIPOLIDINE7.5NO12Bradley & Nicholson (1986)REACTION TIME - Cohoce (CRT)9C-5min1TRIPOLIDINE10NO13ABradley et al. (1987)REACTION TIME - COMPLEX - CRT9C			REACTION TIME - Simple; aud & visual	98	v. brief		HYDROXYZINE	20	YES	
93Pishkin et al. (1983)REACTION TIME, SRT & CRT (Speeded Interference Task); (1983)94Notice1HURORXYZINE (1983)26NO28Cohen et al. (1985)REACTION TIME, SRT & CRT (Speeded Interference Task); (1984)955min1TRIPOLIDINE2.5NO28Cohen et al. (1985)REACTION TIME - Simple, Auditory955min1TRIPOLIDINE2.5NO91Peck et al. (1975)REACTION TIME - Simple, Auditory9515min1TRIPOLIDINE2.5YES22Bye et al. (1977)REACTION TIME - Auditory915min1TRIPOLIDINE5YES28Cohen et al. (1985)REACTION TIME - Simple, Visual955min1TRIPOLIDINE5YES91Peck et al. (1975)REACTION TIME, Simple (SRT); Aud955min1TRIPOLIDINE5YES28Cohen et al. (1985)REACTION TIME, Simple (SRT); Aud955min1TRIPOLIDINE5YES91Peck et al. (1989)REACTION TIME, Simple (SRT) - during ERP958min1TRIPOLIDINE7.5NO12Bradley & Nicholson (1986)REACTION TIME, Cohec (CRT) - during ERP9588min1TRIPOLIDINE10NO13Bradley et al. (1994)REACTION TIME - Cohece (CRT) Leeds9C-5min1TRIPOLIDINE10NO134Bradle				90	v. brief		HYDROXYZINE	20		NO
28Cohen et al. (1985)REACTION TIME - Simple, Visual985 min1 TRIPOLIDINE2.5YES48Hamilton et al. (1982)REACTION TIME - Simple, Auditory985 min1 TRIPOLIDINE2.5YES91Peck et al. (1975)REACTION TIME, Simple (SRT); Aud9815 min1 TRIPOLIDINE2.5YES22Bye et al. (1977)REACTION TIME - Auditory915 min1 TRIPOLIDINE2.5YES28Cohen et al. (1985)REACTION TIME - Auditory915 min1 TRIPOLIDINE5YES28Cohen et al. (1985)REACTION TIME - Simple, Visual9S5 min1 TRIPOLIDINE5YES91Peck et al. (1975)REACTION TIME, Simple (SRT); Aud9S5 min1 TRIPOLIDINE5YES17Swire et al. (1989)REACTION TIME, Simple (SRT) - during ERP9S8 min1 TRIPOLIDINE7.5NO12Bradley & Nicholson (1986)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE10NO18Kerr et al. (1994)REACTION TIME, Choice (CRT) Leeds9C20 trials1 TRIPOLIDINE10NO13ABradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE10NO13BBradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE10NO13BBradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE <t< td=""><td></td><td></td><td></td><td>95</td><td>v. brief</td><td></td><td>I HYDROXYZINE</td><td>20</td><td></td><td>NO</td></t<>				95	v. brief		I HYDROXYZINE	20		NO
48Hamilton et al. (1982)REACTION TIME - Simple, Auditory9815 min1TRIPOLIDINE2.5NO91Peck et al. (1975)REACTION TIME, Simple (SRT); Aud9815 min1TRIPOLIDINE2.5YES22Bye et al. (1977)REACTION TIME - Auditory915 min1TRIPOLIDINE2.5YES28Cohen et al. (1985)REACTION TIME - Auditory915 min1TRIPOLIDINE5YES91Peck et al. (1975)REACTION TIME - Simple, Visual9S5 min1TRIPOLIDINE5YES91Peck et al. (1975)REACTION TIME, Simple (SRT); Aud9S15 min1TRIPOLIDINE5YES917Swire et al. (1989)REACTION TIME, Simple (SRT) - during ERP9S8 min1TRIPOLIDINE7.5NO12Bradley & Nicholson (1986)REACTION TIME - COMPLEX - CRT9C-5 min1TRIPOLIDINE10NO12Remet al. (1994)REACTION TIME, Choice (CRT) Leeds9C20 trials1TRIPOLIDINE10NO13ABradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1TRIPOLIDINE10NO13BBradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1TRIPOLIDINE10NO13BBradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1TRIPOLIDINE10NO				1				25		NO
91Peck et al. (1975)REACTION TIME, Simple (SRT); Aud9515 min1TRIPOLIDINE2.5YES22Bye et al. (1977)REACTION TIME - Auditory915 min1TRIPOLIDINE2.5YES28Cohen et al. (1985)REACTION TIME - Simple, Visual95 min1TRIPOLIDINE5YES91Peck et al. (1975)REACTION TIME, Simple (SRT); Aud9S5 min1TRIPOLIDINE5YES91Peck et al. (1989)REACTION TIME, Simple (SRT) - during ERP9S8 min1TRIPOLIDINE7.5NO12Bradley & Nicholson (1986)REACTION TIME - COMPLEX - CRT9C-5 min1TRIPOLIDINE10NO56Kerr et al. (1994)REACTION TIME - Choice (CRT)9C20 trials1TRIPOLIDINE10NO104Rombaut et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1TRIPOLIDINE10NO138Bradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1TRIPOLIDINE10NO138Bradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1TRIPOLIDINE10NO				И .					YES	
22Bye et al. (1977)REACTION TIME - Auditory915 min1 TRIPOLIDINE2.0YES28Cohen et al. (1985)REACTION TIME - Simple, Visual9S5 min1 TRIPOLIDINE5YES91Peck et al. (1975)REACTION TIME, Simple (SRT); Aud9S5 min1 TRIPOLIDINE5YES117Swire et al. (1989)REACTION TIME, Simple (SRT) - during ERP9S8 min1 TRIPOLIDINE7.5NO12Bradley & Nicholson (1986)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE10NO58Kerr et al. (1994)REACTION TIME - Choice (CRT) Leeds9C20 triale1 TRIPOLIDINE10NO104Rombaut et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE10NO138Bradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE10NO138Bradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE10NO				R .	.8					NO
28Cohen et al. (1985)REACTION TIME - Simple, Visual955 min1 TRIPOLIDINE5YES91Peck et al. (1975)REACTION TIME, Simple (SRT); Aud955 min1 TRIPOLIDINE5YES117Swire et al. (1989)REACTION TIME, Simple (SRT) - during ERP958 min1 TRIPOLIDINE7.5NO12Bradley & Nicholson (1986)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE10NO58Kerr et al. (1994)REACTION TIME - Choice (CRT) Leads9C20 trials1 TRIPOLIDINE10NO104Rombaut et al. (1991)REACTION TIME, Choice (CRT)9Cv. brief1 TRIPOLIDINE10NO13ABradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE10NO13BBradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE10NO13BBradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE10NO				11	8				1	
91 Peck et al. (1975) REACTION TIME, Simple (SRT); Aud 95 15 min 1 TRIPOLIDINE 5 YES 117 Swire et al. (1989) REACTION TIME, Simple (SRT) - during ERP 95 8 min 1 TRIPOLIDINE 7.5 NO 12 Bradley & Nicholson (1986) REACTION TIME, Simple (SRT) - during ERP 95 5 min 1 TRIPOLIDINE 7.5 NO 58 Kerr et al. (1994) REACTION TIME - COMPLEX - CRT 9C -5 min 1 TRIPOLIDINE 10 NO 58 Kerr et al. (1994) REACTION TIME, Choice (CRT) Leeds 9C 20 trials 1 TRIPOLIDINE 10 YES 104 Rombaut et al. (1991) REACTION TIME, Choice (CRT) 9C v. brief 1 TRIPOLIDINE 10 NO 13A Bradley et al. (1987) REACTION TIME - COMPLEX - CRT 9C -5 min 1 TRIPOLIDINE 10 NO 13B Bradley et al. (1987) REACTION TIME - COMPLEX - CRT 9C -5 min 1 TRIPOLIDINE 10 NO 13B Bradley et al. (1987) REACTION TIME - COMPLEX - CRT 9C -5 min 1 TRIPOLIDINE 10 NO </td <td></td> <td></td> <td></td> <td></td> <td>1</td> <td></td> <td></td> <td></td> <td></td> <td></td>					1					
117Swire et al. (1989)REACTION TIME, Simple (SRT) - during ERP9S8 min1 TRIPOLIDINE7.5NO12Bradley & Nicholson (1986)REACTION TIME, Simple (SRT) - during ERP9S8 min1 TRIPOLIDINE7.5NO58Kerr et al. (1994)REACTION TIME - COMPLEX - CRT9C20 trials1 TRIPOLIDINE10NO58Kerr et al. (1994)REACTION TIME - Choice (CRT) Leeds9C20 trials1 TRIPOLIDINE10YES104Rombaut et al. (1991)REACTION TIME, Choice (CRT)9Cv. brief1 TRIPOLIDINE10NO13ABradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE10NO13BBradley et al. (1987)REACTION TIME - COMPLEX - CRT9C-5 min1 TRIPOLIDINE10NO				8					1	
12 Bradley & Nicholson (1986) REACTION TIME - COMPLEX - CRT 9C -5 min 1 TRIPOLIDINE 10 NO 58 Kerr et al. (1994) REACTION TIME - Choice (CRT) Leeds 9C 20 trials 1 TRIPOLIDINE 10 YES 104 Rombaut et al. (1991) REACTION TIME, Choice (CRT) 9C v. brief 1 TRIPOLIDINE 10 NO 13A Bradley et al. (1987) REACTION TIME - COMPLEX - CRT 9C -5 min 1 TRIPOLIDINE 10 NO 13B Bradley et al. (1987) REACTION TIME - COMPLEX - CRT 9C -5 min 1 TRIPOLIDINE 10 NO				11	8				TES	20
58 Kerr et al. (1994) REACTION TIME - Choice (CRT) Leeds 9C 20 trials 1 TRIPOLIDINE 10 YES 104 Rombaut et al. (1991) REACTION TIME, Choice (CRT) 9C v. brief 1 TRIPOLIDINE 10 YES 13A Bradley et al. (1987) REACTION TIME - COMPLEX - CRT 9C v. brief 1 TRIPOLIDINE 10 NO 13B Bradley et al. (1987) REACTION TIME - COMPLEX - CRT 9C -5 min 1 TRIPOLIDINE 10 NO									1	
104 Rombaut et al. (1991) REACTION TIME, Choice (CRT) 9C v. brief 1 TRIPOLIDINE 10 NO 13A Bradley et al. (1987) REACTION TIME - COMPLEX - CRT 9C -5 min 1 TRIPOLIDINE 10 NO 13B Bradley et al. (1987) REACTION TIME - COMPLEX - CRT 9C -5 min 1 TRIPOLIDINE 10 NO				£1					VEC	NO
13A Bradley et al. (1987) REACTION TIME - COMPLEX - CRT 9C -5 min 1 TRIPOLIDINE 10 NO 13B Bradley et al. (1987) REACTION TIME - COMPLEX - CRT 9C -5 min 1 TRIPOLIDINE 10 NO		· ·							123	NO
13B Bradley et al. (1987) REACTION TIME - COMPLEX - CRT 9C ~5 min 1 TRIPOLIDINE 10 NO	13A			ก	1				1	
	13B	Bradley et al. (1987)		8	R					
	continue	d							.	

REACTION TIME TASKS - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only

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continued... Page 2: sorted by Generation, DRUG, Dose, Ref#, SC#.

	. .							IMPAIR	
Ref#	RECERCIÓN	TASK	8. ÷. 8	Chronie	:CO.:	DRUG	e e conservations de la section de la se	₩ <i>6</i> ? ₩	
					2nd	Generation Drugs:			
65	Levander et al. (1991)	REACTION TIME - Choice; visual	90	v, brief	2	CETIRIZINE	10		NO
65	Levander et al. (1991)	REACTION TIME - Simple; aud & visual	8	v, brief		CETIRIZINE	10		NO
95	Ramaekers et al. (1992)	REACTION TIME, Choice (CRT); Stemberg digits	90	10 min		CETIRIZINE	10	YES	1
95	Ramaekers et al. (1992)	Response Competition Test (RCT)	90	15 min		CETIRIZINE	10		NO
100	Riedel et al. (1990)	REACTION TIME, Choice (CRT); Sternberg digits	90		2	CETIRIZINE	10	YES	
6	Betts et al. (1989)	REACTION TIME, Choice (CRT)	90		2	CETIRIZINE	20		NO
6	Betts et al. (1989)	REACTION TIME, Simple (SRT)	95		2	CETIRIZINE	20	YES	
100	Riedel et al. (1990)	REACTION TIME, Choice (CRT); Sternberg digits	90		2	CETIRIZINE	20	YES	
122	Vermeeren et al. (1998)	REACTION TIME, Choice (CRT); Vis (L&R w. distractors)	90	v. brief	2	FEXOFENADINE	120		NO
122	Vermeeren et al. (1998)	REACTION TIME, Choice (CRT); Vis (L&R w. distractors)	90	v, brief	2	FEXOFENADINE	240		NO
37	Englisch et al. (1996)	REACTION TIME - Choice: CRT in ODT	90		2	LORATADINE	10		NO
42	Gaillard et al. (1988)	REACTION TASK - visual field: digits, degraded	9	24 min	2	LORATADINE	10	1	NO
57	Kay et al. (1997)	REACTION TIME - Simple; CogScreen	95	brief	2	LORATADINE	10		NO
95	Ramaekers et al. (1992)	REACTION TIME, Choice (CRT); Sternberg digits	90	10 min	2	LORATADINE	10	1	NO
95	Ramaekers et al. (1992)	Response Competition Test (RCT)	90	15 min	2	LORATADINE	10		NO
109	Schaffler et al. (1994)	REACTION TIME, Choice - CRT (during ODT)	90	dur ODT	2	LORATADINE	10	· ·	NO
6	Betts et al. (1989)	REACTION TIME, Choice (CRT)	90		2	TERFENADINE	60		NO
6	Betts et al. (1989)	REACTION TIME, Simple (SRT)	95		2	TERFENADINE	60		NO
7	Bhatti & Hindmarch (1989)	CHOICE REACTION TIME (CRT)	90	very brief	2	TERFENADINE	60		NO
42	Gaillard et al. (1988)	REACTION TASK - visual field: digits, degraded	9	24 min	2	TERFENADINE	60		NO
58	Kerr et al. (1994)	REACTION TIME - Choice (CRT) Leeds	90	20 trials	2	TERFENADINE	60		NO
61	Kulshrestha et al. (1978)	REACTION TIME - Simple (single light)	98	brief	2	TERFENADINE	60		NO
117	Swire et al. (1989)	REACTION TIME, Simple (SRT) - during ERP	95	8 min	2	TERFENADINE	60		NO
130A	Witek, Jr. et al. (1992)	REACTION TIME, Choice (CRT); Vis	90	v. brief	2	TERFENADINE	60		NO
131A	Witek, Jr. et al. (1995)	REACTION TIME, Choice (CRT); Vis	90	v. brief	2	TERFENADINE	60		NO
6	Betts et al. (1989)	REACTION TIME, Choice (CRT)	90			TERFENADINE	120	1	NO
6	Betts et al. (1989)	REACTION TIME, Simple (SRT)	95			TERFENADINE	120		NO
7	Bhatti & Hindmarch (1989)	CHOICE REACTION TIME (CRT)	90	very brief	_	TERFENADINE	120		NO
74	Murri et al. (1992)	REACTION TIME, Simple (SRT); Vis & Aud	95	brief		TERFENADINE	120		NO
7	Bhatti & Hindmarch (1989)	CHOICE REACTION TIME (CRT)	90	very brief	2	TERFENADINE	240		NO

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TABLE 14. PHYSIOLOGICAL MEASURES - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only

Sheet: PHYSIO.

page 2: sorted by Generation, DRUG, Dose, Ref#, SC#.

	REFERENCE	TASK	8 X - X	Duration	C.	DRUG	Dose: mg		MENT?
			T						·
					1st	Generation Drugs:			
47	Goldstein et al. (1968)	EEG	10	l.	1	CHLORPHENIRAMINE	2		NO
47	Goldstein et al. (1968)	EEG	10		1	CHLORPHENIRAMINE	4	YES	
69	Meador et al. (1989)	ERP - tonal oddball vigilance for P3	10		1	CHLORPHENIRAMINE	8	YES	
83	Nicholson et al. (1991)	Multiple Sleep Latency Test - MSLT	10M	20 min	1	CHLORPHENIRAMINE	8	YES	
63	Lee et al. (1988)	EEG - power spectrum analysis	10	?	1	CHLORPHENIRAMINE	12		NO bP
53	Hopes et al. (1992)	EEG - auditory tones for vigilance	10	20 min?	1	CLEMASTINE	2	YES	
30	Curran et al. (1998)	ERP during Oddball task (auditory - tones)	10	~ 20 min?	1	DIPHENHYDRAMINE	25		NO
30	Curran et al. (1998)	ERP during Word Recognition (visual)	10	~ 20 min?	1	DIPHENHYDRAMINE	25		NO
47	Goldstein et al. (1968)	EEG	10	ų.	1	DIPHENHYDRAMINE	25	YES	
30 30	Curran et al. (1998)	ERP during Oddball task (auditory - tones)	10	~ 20 min?	1	DIPHENHYDRAMINE	50	YES	
	Curran et al. (1998)	ERP during Word Recognition (visual)	10	~ 20 min?	1	DIPHENHYDRAMINE	50	YES	
39 47	Fink et al. (1979)	EEG	10		1	DIPHENHYDRAMINE	50	YES	
101	Goldstein et al. (1968)	EEG	10		1	DIPHENHYDRAMINE	50	YES	
102	Roehrs et al. (1984) Roehrs et al. (1993)	Multiple Sleep Latency Test - MSLT	10M	1 hr	1	DIPHENHYDRAMINE	50	YES	
110	Schweitzer et al. (1993)	Multiple Sleep Latency Test - MSLT	10M	20 min	1	DIPHENHYDRAMINE	50	YES	
114	Simons FE et al. (1996)	Multiple Sleep Latency Test - MSLT	10M	20 min	1	DIPHENHYDRAMINE	50	YES	
119	Tharion et al. (1994)	ERP during Oddball task (auditory - tones)	10	20 min (5mir	1	DIPHENHYDRAMINE	50	YES	
119	Tharion et al. (1994)	ERP - visual patterns (PREP) ERP - auditory (BAEP)	10		1	DIPHENHYDRAMINE	50	YES	
126	Walsh et al. (1994)	Multiple Sleep Latency Test - MSLT	10		1	DIPHENHYDRAMINE	50		NO
115A	Simons KJ et al. (1994)	ERP during Oddball task (auditory - tones)	10M 10	20 min 20 min (5mir	1	DIPHENHYDRAMINE	50	YES	
111	Seidel et al. (1987)	Multiple Sleep Latency Test - MSLT	10M	20 min (Smir 20 min	1 1	DIPHENHYDRAMINE	50	YES	
9	Blom et al. (1992)	EEG - spectral analysis for 5 bands	10	20 11411	1	HYDROXYZINE	25	YES	
115A	Simons KJ et al. (1994)	ERP during Oddball task (auditory - tones)	10	20 min (5mir	1	HYDROXYZINE	30	YES	
82	Nicholson & Stone (1986)	Multiple Sleep Latency Test - MSLT		20 min	1	TRIPOLIDINE	50	YES	
82	Nicholson & Stone (1986)	Multiple Sleep Latency Test - MSLT	10M	20 min	1	TRIPOLIDINE	2.5 5	YES	
83	Nicholson et al. (1991)	Multiple Sleep Latency Test - MSLT	10M	20 min	1	TRIPOLIDINE	5	YES	
117	Swire et al. (1989)	ERP during Oddball task (auditory - tones)	10	8 min	1	TRIPOLIDINE	7.5	TEO	NO
							7.0		NO
					2nd	Generation Drugs:			
114	Simons FE et al. (1996)	ERP during Oddball task (auditory - tones)	10	20 min (5mir	2	ASTEMIZOLE	10		
115A	Simons KJ et al. (1994)	ERP during Oddball task (auditory - tones)	0	20 min (5mir	2	ASTEMIZOLE	10 10		NO
84	Nicholson & Turner (1998)	Multiple Sleep Latency Test - MSLT		20 min	2	CETIRIZINE	5		NO
111	Seidel et al. (1987)	Multiple Sleep Latency Test - MSLT	H .	20 min	2	CETIRIZINE	5		NO NO
84	Nicholson & Turner (1998)	Multiple Sleep Latency Test - MSLT						YES	NU
				1120 min	2		10		
89	Pechadre et al. (1988)	EEG - quantitative, spectral analysis	10	20 min 5 min	2	CETIRIZINE	10 10	150	NO
90	Pechadre et al. (1991)	EEG - quantitative, spectral analysis		20 min 5 min 5 min	2 2 2	CETIRIZINE	10	150	NO
90 95	Pechadre et al. (1991) Ramaekers et al. (1992)	EEG - quantitative, spectral analysis EEG, during Drive	10	5 min	2	CETIRIZINE	10 10		NO NO
90 95 110	Pechadre et al. (1991) Ramaekers et al. (1992) Schweitzer et al. (1994)	EEG - quantitative, spectral analysis EEG, during Drive Multiple Sleep Latency Test - MSLT	10 10	5 min 5 min	2 2	CETIRIZINE	10 10 10	YES	NO
90 95 110 111	Pechadre et al. (1991) Ramaekers et al. (1992) Schweitzer et al. (1994) Seidel et al. (1987)	EEG - quantitative, spectral analysis EEG, during Drive Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT	10 10 10	5 min 5 min 1 hr	2 2 2	CETIRIZINE CETIRIZINE CETIRIZINE	10 10 10 10		NO NO
90 95 110 111 114	Pechadre et al. (1991) Ramaekers et al. (1992) Schweitzer et al. (1994) Seidel et al. (1987) Simons FE et al. (1996)	EEG - quantitative, spectral analysis EEG, during Drive Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT ERP during Oddball task (auditory - tones)	10 10 10 10M	5 min 5 min 1 hr 20 min.	2 2 2 2	CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE	10 10 10 10 10		NO NO NO
90 95 110 111 114 126	Pechadre et al. (1991) Ramaekers et al. (1992) Schweitzer et al. (1994) Seidel et al. (1987) Simons FE et al. (1996) Waish et al. (1994)	EEG - quantitative, spectral analysis EEG, during Drive Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT ERP during Oddball task (auditory - tones) Multiple Sleep Latency Test - MSLT	10 10 10 10M 10M	5 min 5 min 1 hr 20 min 20 min	2 2 2 2 2 2	CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE	10 10 10 10		NO NO NO
90 95 110 111 114 126 33	Pechadre et al. (1991) Ramaekers et al. (1992) Schweitzer et al. (1994) Seidel et al. (1987) Simons FE et al. (1996) Waish et al. (1994) De Roeck et al. (1990)	EEG - quantitative, spectral analysis EEG, during Drive Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT ERP during Oddball task (auditory - tones) Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT	10 10 10 10M 10M 10 10M 10M	5 min 5 min 1 hr 20 min 20 min 20 min (5mir 20 min 20 min	2 2 2 2 2 2 2 2 2 2	CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE	10 10 10 10 10 10		NO NO NO
90 95 110 111 114 126 33 84	Pechadre et al. (1991) Ramaekers et al. (1992) Schweitzer et al. (1994) Seidel et al. (1987) Simons FE et al. (1996) Waish et al. (1994) De Roeck et al. (1990) Nicholson & Turner (1998)	EEG - quantitative, spectral analysis EEG, during Drive Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT ERP during Oddball task (auditory - tones) Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT	10 10 10 10M 10M 10 10M 10M	5 min 5 min 1 hr 20 min 20 min 20 min 20 min 20 min 20 min	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE	10 10 10 10 10 10 10		NO NO NO NO
90 95 110 111 114 126 33 84 111	Pechadre et al. (1991) Ramaekers et al. (1992) Schweitzer et al. (1994) Seidel et al. (1987) Simons FE et al. (1996) Walsh et al. (1994) De Roeck et al. (1990) Nicholson & Turner (1998) Seidel et al. (1987)	EEG - quantitative, spectral analysis EEG, during Drive Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT ERP during Oddball task (auditory - tones) Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT	10 10 10 10M 10M 10M 10M 10M 10M	5 min 5 min 1 hr 20 min 20 min 20 min (5mir 20 min 20 min 20 min	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE	10 10 10 10 10 10 10 20		NO NO NO NO?
90 95 110 111 114 126 33 84 111 90	Pechadre et al. (1991) Ramaekers et al. (1992) Schweitzer et al. (1994) Seidel et al. (1987) Simons FE et al. (1996) Waish et al. (1994) De Roeck et al. (1990) Nicholson & Turner (1998) Seidel et al. (1987) Pechadre et al. (1991)	EEG - quantitative, spectral analysis EEG, during Drive Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT ERP during Oddball task (auditory - tones) Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT EEG - quantitative, spectral analysis	10 10 10 10M 10M 10M 10M 10M 10M 10 10	5 min 5 min 1 hr 20 min 20 min 20 min 20 min 20 min 20 min 20 min 5 min	222222222222222222222222222222222222222	CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE LORATADINE	10 10 10 10 10 10 20 20		NO NO NO NO? NO?
90 95 110 111 114 126 33 84 111 90 95	Pechadre et al. (1991) Ramaekers et al. (1992) Schweitzer et al. (1994) Seidel et al. (1987) Simons FE et al. (1996) Waish et al. (1994) De Roeck et al. (1990) Nicholson & Turner (1998) Seidel et al. (1987) Pechadre et al. (1991) Ramaekers et al. (1992)	EEG - quantitative, spectral analysis EEG, during Drive Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT ERP during Oddball task (auditory - tones) Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT EEG - quantitative, spectral analysis EEG, during Drive	10 10 10 10M 10M 10M 10M 10M 10M 10 10	5 min 5 min 20 min 20 min 20 min 20 min 20 min 20 min 20 min 5 min 1 hr	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE LORATADINE LORATADINE	10 10 10 10 10 10 20 20 20		NO NO NO NO NO NO NO NO
90 95 110 111 114 126 33 84 111 90 95 114	Pechadre et al. (1991) Ramaekers et al. (1992) Schweitzer et al. (1994) Seidel et al. (1987) Simons FE et al. (1996) Waish et al. (1994) De Roeck et al. (1990) Nicholson & Turner (1998) Seidel et al. (1987) Pechadre et al. (1991) Ramaekers et al. (1992) Simons FE et al. (1996)	EEG - quantitative, spectral analysis EEG, during Drive Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT ERP during Oddball task (auditory - tones) Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT EEG - quantitative, spectral analysis EEG, during Drive ERP during Oddball task (auditory - tones)	10 10 10 10M 10M 10M 10M 10M 10M 10 10 10	5 min 5 min 20 min 20 min 20 min 20 min 20 min 20 min 5 min 1 hr 20 min (5mir	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE LORATADINE LORATADINE	10 10 10 10 10 20 20 20 10		NO NO NO NO NO NO NO NO NO
90 95 110 111 114 126 33 84 111 90 95 114 33	Pechadre et al. (1991) Ramaekers et al. (1992) Schweitzer et al. (1994) Seidel et al. (1987) Simons FE et al. (1996) Waish et al. (1994) De Roeck et al. (1990) Nicholson & Turner (1998) Seidel et al. (1997) Pechadre et al. (1991) Ramaekers et al. (1992) Simons FE et al. (1996) De Roeck et al. (1990)	EEG - quantitative, spectral analysis EEG, during Drive Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT ERP during Oddball task (auditory - tones) Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT EEG - quantitative, spectral analysis EEG, during Drive ERP during Oddball task (auditory - tones) Multiple Sleep Latency Test - MSLT	10 10 10 10M 10M 10M 10M 10M 10M 10 10 10 10	5 min 5 min 20 min 20 min 20 min 20 min 20 min 20 min 5 min 1 hr 20 min (5mir 20 min	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE LORATADINE LORATADINE LORATADINE	10 10 10 10 10 20 20 20 10 10		NO NO NO NO NO NO NO NO NO NO NO NO NO N
90 95 110 111 114 126 33 84 111 90 95 114 33 90	Pechadre et al. (1991) Ramaekers et al. (1992) Schweitzer et al. (1994) Seidel et al. (1987) Simons FE et al. (1996) Waish et al. (1994) De Roeck et al. (1994) De Roeck et al. (1990) Nicholson & Turner (1998) Seidel et al. (1987) Pechadre et al. (1991) Ramaekers et al. (1990) De Roeck et al. (1990) Pechadre et al. (1991)	EEG - quantitative, spectral analysis EEG, during Drive Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT ERP during Oddball task (auditory - tones) Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT Multiple Sleep Latency Test - MSLT EEG - quantitative, spectral analysis EEG, during Oddball task (auditory - tones) Multiple Sleep Latency Test - MSLT EEG - quantitative, spectral analysis	10 10 10 10M 10M 10M 10M 10M 10 10 10 10M 10	5 min 5 min 20 min 20 min 20 min 20 min 20 min 20 min 5 min 1 hr 20 min (5mir	222222222222222222222222222222222222222	CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE CETIRIZINE LORATADINE LORATADINE LORATADINE LORATADINE LORATADINE	10 10 10 10 10 20 20 20 20 10 10 10 20 20		NO NO NO NO NO NO NO NO NO NO NO
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Note: 100% of findings for 1st generation drugs (9/9 vs 1/11=9.1% for 2nd gen.) showed significant sedation as measured by MSLT (SC# 10M). EEG and ERP findings (SC# 10) were more variable, resulting in 68.4% "YES" significant impairment in 1st generation drugs (13/19) vs 17.6% in 2nd generation drugs (3/17).

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Overall (SC# 10, 10M), the Physiological measures of sedation demonstrated significant impairment in 78.6% 1st generation drugs vs 14.3% 2nd gen.

Appendix B

EXAMPLE of an Impairment Summary Sheet

YES/NO Counts by Behavioral Category

DRIVING-RELATED SKILLS PERFORMANCE IMPAIRMENT as a function of ANTIHISTAMINE (Drug/Dose), TASK CATEGORY and DOSING (Acute/Repeated).

	05-10+ 10,15,20	4 1 3 75.0%				
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rrate studies as reported in 130 scientific papers. * "TEST" = an experimental test of a given drug, dose, and task messure; "YES" = statistically significant impeliment relative to Placebo (p < 0.05) Tota : unrecovorume	24.25 E	C O O O	HYDROXYZINE across dose #tests: 0 #TO: 0 #YES: 0 %YE8: ERR	22		<u> </u>
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	DRUG CODE &	23 #tests: 1 12 #NO: 0 11 #YES: 100.0%		2nd generation: Drug cope a Mi	32 #tests: 28 #NO: 4 #YES: 12.6% %YE8	
Resulta IASK CA DRIVIN SC#: Roed, C 1st gen	DRUG	47.8		2nd g Drug		

79

RESULTS in above table are from the following studies; REFERENCE numbers of research articles are shown:

Re译: see master list for SCH: 1 (1R,1C,1S,17)

Appendix C

EXAMPLE of a Study Summary Sheet

(Note: A Study Summary Sheet was generated for each of n=138 studies from the 130 references. Copies are available from the authors upon request.)

Fex 240mg improve drive & attenuate alc impair Sine fine Line Ione 20m Dosing: A=Acute, R=Repetted, Resid=Residual effects COMMENTS. Train: sep day; clemastine 2mg bid (h.s., AM day1) coded as 3mg Acute & 4mg R; F120,240AM, so A; F120bid, F60bid, so R: 240, 120mg; fexo improved drive & attentuated alc impair, but sig impair CTTI D6: TRIPOLIDINE RESULTS: DID STUDY SHOW STATISTICALLY SIGNIFICANT IMPAIRMENT (relative to Placebo) as function of DRUG (and DOSE) SHOWN BELOW? Alerting effects? 10ms 20.25ms 30ms 50ms D4: HYDROXYZINE Residual IF study also included ALCOHOL treatment, coded results below reflect No Alcohol (or Placebo drink) conditions for test of drug alone effects NG: TERFENADINE me 120mg 240m Acute Repeat Day 1 Day4, 5+atc 50mg 25.100 150mg 200+mg CODES: Blind: DB=Double-blind. SB=Single-blind PC+: Positive control; Coded for 10 key drugs or other 1st (D) or 2nd (N) generation H1-entagonists or Miso: drugs (M) D3: DIPHENHYDRAMINE NA: LORATADINE TEST duration 1hr perf, 1hr drive Ome 20mg N3: FEXOFENADINE 2 2 2 2 2 2 2 **2** 120mg 240mg 200 PostDose 1.5h perf,+3drive YES Ŷ ş ş YES 2 2 2 2 2 2 2 2 2 DI: CHLORPHENIRAMINE DZ: CLEMASTINE Ņ YES 200 2005 £ YES N2: CETIRIZINE in itm 20m TITLE Fexofenadine's effects, alone and with alcohol, on actual driving and psychomotor performance E AGE (M) Population 31.5 + 8.5 Healthy volunteers 2.4mg Smg 8.10 12mg 18mg One 20me 30me 40me N1: ASTEMIZOLE R Resid. A R Resid. <u>AGES</u> 21 - 45 × × × × × × × × • × × × × × × <u>Males (n)</u> 12 **TaskDUR** TaskDUR v. brief v. brief v. brief v. brief 45 min 45 min C. String
 C. String <u>ال</u> v, brief 45 min 1 45 min ŧ ÷ Se (n) 24 [N=No, Y=Yes] **ö ö** g ğ REACTION TIME, Choice (CRT); Via (L&R w. dr 9C ₩ ₩ SOURCE J Allergy Clin Immunol REACTION TIME, Choice (CRT); Ms (L&R w. di 9C ິຊູ REACTION TIME, Chalos (CRT); Via (L&R. w. dt 9C REACTION TIME, Chalos (CRT); Via (L&R. w. dt 9C ξ ξ VIGILANCE - Sustained Attention - - SCRI (45m 7 VIGILANCE - Sustained Attention - -- SCRI (46m 7 VIGILANCE - Sustained Attention - -'SCRI (45m 7 VIGILANCE - Sustained Attention - -- SCRI (45m 7 DESIGN Cross x6 RESULTS TASK (or Subjective SEDATION) CRITICAL TRACKING (CTT) - -SCRI (5 blain) CRITICAL TRACKING (CTT) - -SCRI (5 Main) TASK (or Subjective SEDATION) CRITICAL TRACKING (CTT) - -SCRI (5 Main) CRITICAL TRACKING (CTT) - ~SCRI (5 Mate) VOL:PP 101: 306-311 DRIMING - Actual, Highway circult DRIMING - Actual, Highway circul DRIVING - Actual, Highway circuit DRIVING - Actual, Highway circult ALCOHOL? Y ŝ 80 σ ₽ 1 ŝ G ø **G** METHOD 81

SC#: Skiil Cathegory: #1-Drive & Fyre: 2-Psychemeter, 3-Psychemeter, 5-Coprise St#s; 5-Drives St#s; 5-Drived Attender; 7-Nglance; 5-Tracking: P-Readen Time; 10-Physiologica (ASLT, EEG, ERP); 90-Subjective Sedation

STUDY SUMMARY SHEET

AUTHORS Vermeeren A, O'Hanlon JF.

REF# 122 YEAR 1998

CITATION

CITATION

STUDY SUMMARY SHEET: Page 2 of 2

REF# 122 YEAR 1998 AUTHORS Vermeeren A, O'Hanlon JF.

COMMENTS: n=24;driving & psychomotor perf; day1,4 &alc day5; O'Hanlon; issue: Fex impair CTT acute dose; improve drive & attenuate alc impair; alerting effect?

RESULTS - Continued... COMMENTS for each line of study results:

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A R Reski. COMMENTS: X CTT: C3acute sig (Dey 1 AM dose, and h.s. dose: C2mg bid); F120,240 as AM doses both sig impair!	CTT: n.s. Day4; but alc sig impaired, and C and F240 (AM dose) +alc sig > alc atone	CXT: It is any time or drug dose, but are egy imparted	CRT: n.s any time or drug dose; but alc sig impaired	VIG: n.e. any time or drug does, but C trend impair Day $1(p=.075)$; alc sig impaired	VIG: n.s. any time or drug dose, but C trend impair Day1(p =.075); alc sig impaired	DRIVE: C sig impeired Day 1&4; n.s. 7 effect on Day1	DRIVE: C sig impaired Dey 184; T240mg (h.s/AW) sig improved driving Day4 & F240 (both dose regs) sig atten alc impairi!										
Resid.																	
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RESULTS IASK (or Subjective SEDATION) 1 cumcar Tracking (ctt)ScRI (5 mea)	2 CRITICAL TRACIONO (CTT) - ~SCRI (5 trais)	3 REACTION TIME, Choice (CRT); Via (L&R w. distractor 9C	4 REACTION TIME, Choice (CRT); Vis (L&R w. distractor 9C	5 VIGILANCE - Sustained Attention - ~ SCRI (45min)	6 VIGILANCE - Sustained Attention - ~'SCRI (45mtn)	7 DRIVING - Actual, Highway circult	8 DRIVING - Actual, Highway circuit	5	10	11	12	13	14	15	16	17	18

Appendix D

Summary Table of Impairment Findings by Study (includes all 10 Drugs)

APPENDIX D Summary Table of Impairment Findings by Study

YES/NO indicates whether or not at least one finding of significant impairment (or sedation) was reported in the study. Empty columns for any of the 10 drugs, D1-D5 and N1-N5, indicate that the given drug was not evaluated in that study. See end of this table for notes concerning reference numbers and drug codes shown.

LC? (Y	=Yes,	ED STUDY N=No) indicates if stu alcohol as a treatment							2 GENERATION DRUGS						
ef#	YEAR	AUTHOR	ALC?	D1	D2	D3	D4	D5	N1	N2	N3	N4	N5		
1	1989	Alford C, et al.	N	YES				YES		NO			NO		
2	1989	Aso T, et al.	N	YES									NO		
3	1983	Bateman DN, et al.	Y						NO						
4	1982	Berlinger WG, et al.	N			YES									
5	1984	Betts T, et al.	N					YES					NO		
6	1989	Betts T, et al.	N							YES			NO		
7	1989	Bhatti JZ, et al.	Y										YES		
8	1979	Biehl B	N	YES											
		Blom MW, et al.	N				YES								
11	1988	Borbely AA, et al.	N			x-NO									
12	1986	Bradley CM, et al.	N					YES							
		Bradley CM, et al.	N					YES							
14	1987	Bradley CM, et al.	N					YES				YES			
15	1993	Brookhuis KA, et al.	N					YES							
16	1990	Burns M	Y			YES									
17	1980	Burns M, et al.	Y			YES									
18	1993	Burns M, et al.	N			YES							NO		
19	1994	Burns M, et al.	N			YES									
20	1998	Burns M, et al.	N			YES									
21	1974	Bye C, et al.	N					YES							
		Bye C, et al	N					YES							
23	1995	Caldwell J	N			YES							NO		
24	1978	Carruthers SG, et al.	N			YES									
25	1982	Chapman PH, et al.	N	YES					NO						
		Clarke CH, et al.	N	YES	YES								NO		
		Cohen AF, et al.	N			YES									
28	1985	Cohen AF, et al.	N					YES							
		Cohen AF, et al.	Y			YES							х		
-29	1987	Cohen AF, et al.	Υ Ι			YES									

<u>30</u> 31 32	<u>1998</u> <u>1972</u> <u>1986</u> <u>1990</u>	AUTHOR Curran HV, et al. Day ES, et al.	ALC?	D1	D2						ATION iS		
31 32	1972 1986 1990	Day ES, et al.	N			<u>D3</u>	D4		N1	N2	<u>N3</u>	N4	N5
32	<u>1986</u> 1990	-				YES							l
32	<u>1986</u> 1990	-	N		NO								
	1990	De Gier JJ, et al.	N						NO				
		De Roeck J, et al.	N			NO				NO		NO	
34	1986	Dhorranintra B, et al.	N						NO				
35	1990	Dhorranintra B, et al.	N	YES									
36	1988	Doms M, et al.	Y							NO			
37	1996	Englisch W, et al.	N									NO	
38	1994	Fine BJ, et al.	N			YES							
39	1979	Fink M, et al.	N	_		YES							NO
40	1978	Franks HM, et al.	Y	YES									
41	1979	Franks HM, et al.	Y		NO								
42	1988	Gaillard AW, et al.	N		YES							YES	YES
43	1987	Gengo FM, et al.	N				YES			NO			
44	1990	Gengo FM, et al.	N			YES				YES			
45	1989	Goetz DW, et al.	N				YES						NO
46	1991	Goetz DW, et al.	N				YES						NO
47	1968	Goldstein L, et al.	N	YES		YES							
48	1982	Hamilton M, et al.	N					NO					
49	1976	Hindmarch I	N		NO								
50	1978	Hindmarch I, et al.	N	YES	NO								
51	1986	Hindmarch I, et al.	N						NO				
		Hopes H, et al.	N		YES								
		Hughes FW, et al.	Y			YES							
55	1992	Irving A, et al.	Y					NO					
		Katz IR, et al.	N			YES							
		Kay GG, et al.	N			YES						NO	
		Kerr JS, et al.	N					YES					YES
		Khosla PP, et al.	N	YES									
		Kohl RL, et al.	N						YES				
		Kulshrestha VK, et al.	N	YES									NO
		Ledin T, et al.	N		NO							NO	
		Lee A, et al.	N	YES									
		Levander S, et al.	N		YES		YES						

ALC? ()	/=Yes,	ED STUDY N=No) indicates if stu- alcohol as a treatment	dy effect.						2	ATIO IS	Ń		
Ref#	YEAR	AUTHOR	ALC?	D1	D2	D3	D4	D5	N1	N2	N3	N4	N5
65	1991	Levander S, et al.	N				YES						
66	1997	Lines C, et al.	N			YES							
67	1973	Linnoila M	Y			NO							
68	1986	Mattila MJ, et al.	N			YES							
		Meador KJ, et al.	N	YES									NO
70	1978	Mohs RC	N			YES							
71	1978	Moser L, et al.	Y			YES							NO
73	1988	Moskowitz H, et al.	N			YES							NO
74	1992	Murri L, et al.	N										NO
75	1992	Neves-Pinto RM, et al.	N									NO	
76	1979	Nicholson AN	N	NO				YES					
77	1982	Nicholson AN, et al.	N					YES	NO				NO
78	1982	Nicholson AN, et al.	N					YES	NO				NO
79	1983	Nicholson AN, et al.	N					YES					NO
80	1984	Nicholson AN, et al.	N					YES					
81	1985	Nicholson AN, et al.	N					x-NO					
82	1986	Nicholson AN, et al.	N					YES					NO
83	1991	Nicholson AN, et al.	N	YES				YES					
84	1998	Nicholson AN, et al.	N							YES			
85	1992	Offenloch K, et al.	N										NO
86	1988	O'Hanlon JF	Y					YES				NO	NO
87	1994	Patat A, et al.	N		YES								
88	1995	Patat A, et al.	Y							YES			
89	1988	Pechadre JC, et al.	N							NO			YES
90	1991	Pechadre JC, et al.	N							NO		YES	
91	1975	Peck AW, et al.	N		YES			YES					
92	1993	Philpot EE, et al.	N	YES		YES							NO
93	1983	Pishkin V, et al.	N		YES	NO	NO						
1		Preston KL, et al.	N			YES							
95	1992	Ramaekers JG, et al.	Y							YES		NO	
96	1994	Ramaekers JG, et al.	N			YES							YES
97	1978	Reinberg A, et al.	N		YES								NO
98	1993	Rice VJ, et al.	N			YES			NO				
99	1990	Riedel WJ, et al.	Y					YES				NO	NO
100	1990	Riedel WJ, et al.	Y							YES			

		N=No) indicates if stu alcohol as a treatment							2	-		-	IN
Ref#	YEAR	AUTHOR	ALC?	D1	D2	D3	D4	D5	N1	N2	N3	N4	N5
101	1984	Roehrs TA, et al.	N			YES							
102	1993	Roehrs TA, et al.	Y			YES							
103	1993	Roehrs TA, et al.	Y			YES							
104	1991	Rombaut N, et al.	N					YES					
105	1987	Roth T, et al.	N			YES						YES	
		Saarialho-Kere U, et											
	1989		N										
		Saletu B, et al.	N			x-NO							
		Sands L, et al.	N			YES							
109	1994	Schaffler K, et al.	N									NO	
110	1994	Schweitzer PK, et al.	N			YES				NO			<u> </u>
111	1987	Seidel WF, et al.	N				YES			NO			
112	1981	Seppala T, et al.	N		YES								
113	1982	Seppala T, et al.	N						NO				
114	1996	Simons FE, et al.	N			YES			NO	YES		NO	NO
115	1994	Simons KJ, et al.	N			YES	YES			NO			
116	1980	Spector R, et al.	N			YES							
		Swire FMM, et al.	N					YES					NO
		Tharion WJ, et al.	N			YES							NO
		Unchern S, et al.	N	YES		YES							NO
		Valk PJ, et al.	N					YES				NO	
		Vermeeren A, et al.	Y		YES					ĺ	YES		
		Volkerts ER, et al.	N			ĺ		YES		NO			YES
		Vuurman EF, et al.	N		YES								
		Walsh JK, et al.	N				YES			NO			
		Walsh JK, et al.	N			YES			ĺ	NO			
		Wilkinson CJ, et al.	Y			YES						NO	
		Wilkinson CJ, et al.	Y			NO						NO	
		Wilkinson CJ, et al.	N			YES							
		Witek TJ, Jr., et al.	N		ĺ	YES			İ	İ	İ		NO
		Witek TJ, Jr., et al.	N	YES	ĺ	YES			İ	İ	İ		NO
		Yasuda SU, et al.	N	YES						İ			
	1998		N	120								NO	
		Scavone JM, et al.	N			NO							
104	1990	ocavone JIVI, et al.											

NOTES: See following page for notes for table presented above.

APPENDIX D

Summary Table of Impairment Findings by Study

Continued...

Notes: Results for review were limited to n=134 references (REF# shown above) which actually reflect 138 separate studies since some references reported more than one study. Also, of the indexed n=134 studies, four were excluded: #10,#52,#72,#118.

Studies limited to findings for residual effects only are noted above with an "x" prefix, eg. "x-NO".

1st GENERATION DRUGS:

D1=chlorpheniramine, D2=clemastine, D3=diphenhydramine, D4=hydroxyzine, D5=tripolidine.

2nd GENERATION DRUGS:

N1=astemizole, n2=cetirizine, N3=fexofenadine, N4=loratadine, N5=terfenadine.

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