(25)

BRIEFING ON BENZODIAZEPINE SLEEP-INDUCING COMPOUNDS

I. (Introduction as appropriate) GOOD MORNING, I AM CPT VINCE O'DONNELL, CHIEF OF THE HUMAN PSYCHOPHARMACOLOGY BRANCH, DEPT. OF BEHAVIORAL BIOLOGY, WRAIR. WITH ME TODAY ARE LTC GREG BELENKY, THE CHIEF OF THE DEPARTMENT OF BEHAVIORAL BIOLOGY AND DR. JAMES ANDRADE A CONTRACTOR FROM HOWARD UNIVERSITY'S DEPARTMENT OF PSYCHOLOGY. WHILE I WILL BE MAKING THE INITIAL PRESENTATION HERE, I SHOULD INDICATE THAT THE PRESENTATION REPRESENTS THE JOINT EFFORTS OF THE THREE OF US.

II. (purpose) THE PURPOSE OF THIS PRESENTATION IS TO PROVIDE INFORMATION ON A RESEARCH PROGRAM TO SUPPORT THE FIELDING OF SLEEP-INDUCING COMPOUNDS.

III. (background) THE HUMAN PSYCHOPHARMACOLOGY BRANCH, A NEW ELEMENT OF THE DEPARTMENT OF BEHAVIORAL BIOLOGY, DIVISION OF NEUROPSYCHIATRY, WRAIR, IS BEING ESTABLISHED TO CONDUCT RESEARCH ON THE PERFORMANCE EFFECTS OF PRESCRIBED MEDICATIONS. A MAJOR THRUST OF THAT RESEARCH PROGRAM IS THE IDENTIFICATION AND EVALUATION OF DRUGS TO SUSTAIN OR ENHANCE MILITARY PERFORMANCE IN THE FACE OF DEGRADATION FACTORS. ONE SPECIFIC AREA OF RESEARCH WITHIN THIS PROGRAM IS THE PHARMACOLOGIC CONTROL OF SLEEP AND AROUSAL STATES THROUGH THE FIELDING OF A DRUG TO PROMOTE RAPID SLEEP IN SOLDIERS AT CRITICAL TIMES SUCH AS DURING BREAKS IN COMBAT OPERATIONS OR DURING LONG AIR FLIGHTS AT THE INITIATION OF RAPID DEPLOYMENT

MISSIONS.

IV. AFTER A THOROUGH REVIEW OF THE LITERATURE IT IS OUR RECOMMENDATION THAT THE SHORT ACTING BENZODIAZEPINE TRIAZOLAM IN A DOSE OF 0.25 MG IS THE MOST SUITABLE DRUG IMMEDIATELY AVAILABLE IN THIS COUNTRY FOR USE AS A SLEEP INDUCING AGENT IN MILITARY OPERATIONS. THE FOLLOWING IS A DISCUSSION OF THE REASONS FOR THIS RECOMMENDATION WITH ATTENTION TO QUESTIONS THAT MUST STILL BE ANSWERED ABOUT THE USE OF TRIAZOLAM, AND WITH SUGGESTIONS FOR FUTURE RESEARCH DIRECTIONS.

V. IN EVALUATING SLEEP-INDUCING DRUGS IN THIS CONTEXT, WE OPERATED ON THE ASSUMPTION THAT FOR A DRUG TO BE FIELDED IMMEDIATELY, IT WOULD HAVE TO:

(viewgraph 1)

BE CURRENTLY APPROVED FOR USE AS A HYPNOTIC IN THIS COUNTRY;

BE COMMERCIALLY AVAILABLE IN AN APPROPRIATE ORAL UNIT DOSE.

NUMEROUS DRUGS WERE REVIEWED FOR COMPARISON PURPOSES AND FOR FUTURE PROGRAMMATIC CONSIDERATION, BUT ONLY THOSE DRUGS MEETING THE ABOVE TWO RESTRICTIONS WERE CONSIDERED AS

CANDIDATES FOR IMMEDIATE FIELDING.

VI. THE FOLLOWING ARE THE DRUGS AND DRUG CLASSES THAT WERE INITIALLY CONSIDERED IN OUR REVIEW:

(viewgraph 2)

A. BENZODIAZEPINES

B. ANTI-HISTAMINES

C. BARBITURATES

D. CHLORAL HYDRATE AND CHLORAL BETAINE

E. NEUROPEPTIDES (E.G. DSIP, SUBSTANCE S)

F. ETHCHLORVYNOL (p. 363 G&G)

G. ETHINAMATE (A RELATIVELY NEW HYPNOTIC--IT IS A URETHANE; THE MECHNAISM OF ACTION IS UNKNOWN)

VII. ALL DRUG CLASSES EXCEPT THE BENZODIAZEPINES APPEAR UNSUITABLE FOR IMMEDIATE MILITARY USE AS HYPNOTICS. SOME OF THE REASONS FOR REJECTION OF PARTICULAR DRUGS AND DRUG CLASSES ARE AS FOLLOWS:

(viewgraph 3)

(?unless otherwise noted, behavioral data in Johnson article)

A. ANTI-HISTAMINES: WHILE THE ANTIHISTAMINE BENADRYL (diphenhydramine) WAS USED AS A HYPNOTIC WITH SUCCESS BY THE ISRAELIS ON THE ENTEBBE RAID, IT AND THE OTHER ANTIHISTAMINES POSE A NUMBER OF POTENTIAL PROBLEMS INCLUDING PARADOXICAL AROUSING REACTION IN SOME SUBJECTS; SUBSTANTIAL POTENTIATION OF ANTICHOLINERGICS AND A NUMBER OF UNCOMFORTABLE PHYSICAL EFFECTS.

B. BARBITURATES: HIGH ABUSE POTENTIAL; NEGATIVE PERFORMANCE EFFECTS FOLLOWING SLEEP; RELATIVELY HIGH POTENTIAL FOR ADVERSE PHYSICAL REACTIONS; SOME HAVE SUBSTANTIAL POTENTIATION OF ANTICHOLINERGICS; SOME HAVE UNUSUALLY WIDE VARIATION IN ABSORPTION FROM GASTROINTESTINAL TRACT

C. CHLORAL HYDRATE AND CHLORAL BETAINE: ABUSE POTENTIAL; POTENTIAL FOR ADVERSE PHYSICAL AND BEHAVIORAL EFFECTS INCLUDING SOMNAMBULISM; PARADOXICAL AROUSING REACTION IN SOME SUBJECTS.

D. ETHCHLORVYNOL: ABUSE POTENTIAL; SIGNIFICANT ADVERSE PERFORMANCE EFFECTS INCLUDING PRODUCTION OR

AGGRAVATION OF DEPRESSION;

E. ETHINAMATE THERE IS RELATIVELY LITTLE DATA AVAILABLE ON THE EFFICACY OF ETHINAMATE, FOR EXAMPLE THE LETHAL DOSE IS NOT WELL DEFINED AND WE DO NOT KNOW ITS EFFECT ON SLEEP ARCHITECTURE; WE DO KNOW THAT IT PRODUCES A PARADOXICAL AROUSING REACTION IN SOME SUBJECTS, AND THAT IT IS ASSOCIATED WITH A NUMBER OF ADVERSE PHYSICAL EFFECTS INCLUDING NAUSEA, VOMITING, AND RASH; (?see Goodman and gilman, p. 368-369, 908 in PDR);

F. NEUROPEPTIDES: NOT CURRENTLY AVAILABLE FOR USE IN THIS COUNTRY; RELATIVELY LITTLE HUMAN DATA;

IN ADDITION TO THE SPECIFIC REASONS ENUMERATED ABOVE, MANY OF THE REJECTED DRUGS HAVE MECHANISMS OF ACTION WHICH ARE EITHER EXTREMELY DIVERSE OR NOT UNDERSTOOD. WITHOUT A SPECIFIC AND DEFINED MECHANISM OF ACTION, IT IS HIGHLY IMPROBABLE THAT A SAFE AND EFFECTIVE COUNTER-MEDICATION FOR THE EMERGENCY AROUSAL OF SEDATED SOLDIERS COULD BE DEVELOPED. SINCE ANY SLEEP INDUCING DRUG WILL ALMOST CERTAINLY PRODUCE NEGATIVE PERFORMANCE EFFECTS DURING THE PEAK OF ITS ACTION, THE DEVELOPMENT OF A COUNTER-MEDICATION IS VITAL IF THE APPLICABILITY OF A SLEEP-INDUCING DRUG IS TO BE EXTENDED TO FIELD SITUATIONS WHERE SOLDIERS CANNOT COUNT ON A SIX HOUR PERIOD OF UNINTERRUPTED SLEEP. A CONSIDERABLE BODY OF LITERATURE IS

ACCUMULATING ON THE DEVELOPMENT OF BENZODIAZEPINE ANTAGONISTS WHICH APPEAR TO BE ABLE TO SPECIFICALLY COUNTER THE SLEEP-INDUCING PROPERTIES OF THE BENZODIAZEPINES WITHOUT PRODUCING SUBSTANTIAL PERFORMANCE DEFICITS.

THUS BENZODIAZEPINES ARE THE DRUG CLASS OF CHOICE AND THIS GROUP WAS EXAMINED IN DETAIL.

VIII. BENZODIAZEPINES HAVE TRADITIONALLY BEEN GROUPED ACCORDING TO THEIR PLASMA HALF-LIFE. THIS TRADITIONAL GROUPING HAS GIVEN RISE TO INTERPRETATIVE PROBLEMS. WHILE SOME HAVE ASSERTED THAT A SHORT PLASMA HALF-LIFE INDICATES A CORRESPONDINGLY SHORT DURATION OF ACTION, A GROWING BODY OF LITERATURE INDICATES FREQUENT DISSOCIATION BETWEEN THE DURATION OF BEHAVIORAL EFFECTS AND THE PLASMA HALF-LIFE. OBVIOUSLY FOR THE PURPOSE CONSIDERED HERE, WE MUST BE INTERESTED IN THE TIME COURSE OF BENZODIAZEPINE'S EFFECTS ON SLEEP AS A MAJOR PARAMETER, WITH ATTENTION TO INITIAL SLEEP LATENCY, TOTAL DURATION OF SLEEP, SPONTANEOUS AWAKENINGS FROM SLEEP, RETURN TO SLEEP LATENCY, AND SLEEP STAGE ALTERATIONS. IN ADDITION, THE TIME COURSE OF PERFORMANCE DEGRADATION IS CRITICAL. MOST REPORTED BEHAVIORAL DECREMENTS SUBSEQUENT TO BENZODIAZEPINE ADMINISTRATION FALL INTO TWO CATEGORIES: MEMORY AND PSYCHOMOTOR. OF THE LATTER, WHICH CONSIST OF TASKS THAT HAVE SIGNIFICANT MENTAL AND MOTOR COMPONENTS (E.G. CARD SORTING, SYMBOL COPYING, ETC.) THE TASKS THAT ARE MOST DECREMENTED ARE

THOSE THAT HAVE A REQUIREMENT FOR THE SUBJECT TO PERFORM RAPIDLY. SIMILARLY, THE MOST LIKELY MEASURE OF ANY TASK TO SHOW A DECREMENT IS THE TIME TAKEN TO COMPLETION. AS I HAVE PREVIOUSLY STATED, THE TEMPORAL RELATIONSHIP BETWEEN ANY OR ALL OF THESE BEHAVIORAL EFFECTS AND THE PLASMA CLEARANCE RATES MAY BE ONLY BE LOOSELY CORRELATED.

A LESS PROFOUND PROBLEM IS THE LACK OF CONSISTENCY IN HALF-LIFE DESIGNATORS. SINCE BRIEF DURATION OF ACTION HAS BECOME HIGHLY DESIRABLE FOR MANY USES OF THE DRUGS, THE LABELING OF THESE DRUGS HAS OFTEN MIMICKED THE SUPERMARKET'S USE OF SUPER ECONOMY, JUMBO, AND GIANT SIZE DESIGNATIONS TO STAND FOR LARGE, MEDIUM, AND SMALL. WE NOW FIND BENZODIAZEPINES BEING DESCRIBED AS ULTRA-SHORT, SHORT, AND INTERMEDIATE-SHORT ACTING DRUGS.

BECAUSE CLASSIFICATION BY HALF-LIFE CONTINUES TO BE COMMON, WE WILL USE THIS CLASSIFICATION IN OUR DISCUSSION. OUR CATEGORIES ARE SHORT HALF LIFE—LESS THAN 5 HOURS—, INTERMEDIATE HALF LIFE—5 TO 24 HOURS—, AND LONG HALF LIFE—GREATER THAN 24 HOURS—. THIS MAY BE SOMEWHAT DIFFERENT FROM THE TERMINOLOGY USED BY THE PHARMACEUTICAL HOUSES FOR ANY GIVEN DRUG.

GIVEN OUR CLASSIFICATION SCHEME, THE FOLLOWING ARE SOME REPRESENTATIVE BENZODIAZEPINES THAT WERE REVIEWED FOR THEIR POTENTIAL AS MILITARY HYPNOTICS:

(viewgraph 4)

I. SHORT HALF LIFE (< 5 HOURS)

TRIAZOLAM MIDAZOLAM

II. INTERMEDIATE HALF LIFE (5 TO 24 HOURS)

NITRAZEPAM FLUNITRAZEPAM CLOBAZAM* LORAZEPAM TEMAZEPAM
BROMAZEPAM ESTRAZOLAM ALPRAZOLAM OXAZEPAM LOPRAZOLAM
LORMETAZEPAM

III. LONG HALF (> 24 HOURS)

CHLORDIAZEPOXIDE DIAZEPAM FLURAZEPAM

*CLOBAZAM IS METABOLIZED LIKE A LONG HALF LIFE BENZODIAZEPINE, BUT ITS PHYSIOLOGICAL AND BEHAVIORAL EFFECTS ARE THOSE OF AN INTERMEDIATE HALF LIFE BENZODIAZEPINE

IX. IN ADDITION TO CURRENT FDA APPROVAL AS A HYPNOTIC, THE

FOLLOWING QUALITIES WERE SOUGHT:

(viewgraph 5)

A. EFFECTIVE HYPNOTIC (SLEEP-INDUCING) PROPERTIES

B. RAPID ONSET OF HYPNOTIC EFFECT

C. SHORT DURATION OF HYPNOTIC EFFECT (ABOUT SIX HOURS)

D. EASY AROUSAL FROM DRUG-INDUCED SLEEP

E. LACK OF NEGATIVE EFFECTS DURING PERIOD OF THE DRUG'S HYPNOTIC ACTION

F. LACK OF NEGATIVE EFFECTS AFTER THE PERIOD OF THE DRUG'S HYPNOTIC ACTION

G. LOW ABUSE POTENTIAL

(***go to viewgraph 6 before speaking***)

X. ON THIS VIEWGRAPH IS A MATRIX SHOWING THE CHARACTERISTICS DESIRED IN A HYPNOTIC DRUG FOR MILITARY APPLICATION AS THEY APPLY TO REPRESENTATIVES OF THE THREE CLASSES OF

BENZODIAZEPINES REVIEWED HERE. NOTE THAT ALL OF THESE DRUGS WILL INDUCE SLEEP AT SOME DOSE, SO NO DIFFERENTIATION IS OFFERED ON THE BASIS OF HYPNOTIC EFFICACY.

THE HEADING "LOW ACUTE NEGATIVE EFFECTS" REFERS TO ADVERSE PERFORMANCE EFFECTS SUCH AS PROBLEMS WITH MEMORY, REACTION TIME, AND SPEED ON MENTAL AND PHYSICAL TASKS, EXPERIENCED WITHIN SIX HOURS AFTER DRUG ADMINISTRATION.

THE HEADING LOW RESIDUAL NEGATIVE EFFECTS REFERS TO ADVERSE PERFORMANCE EFFECTS EXPERIENCED MORE THAN SIX HOURS AFTER DRUG ADMINISTRATION.

NOTE THAT ALL HEADINGS ARE PHRASED IN SUCH A FASHION THAT A YES ENTRY IN THE MATRIX INDICATES A DESIRABLE CHARACTERISTIC; A NO INDICATES AN UNDERSIRABLE CHARACTERISTIC. A QUESTION MARK INDICATES EITHER UNKNOWN INFORMATION OR THAT A SIGNIFICANT CONTROVERSY EXISTS IN THE LITERATURE.

(***leave viewgraph on***)

XL TRIAZOLAM HAS BEEN DEMONSTRATED TO BE AN EFFECTIVE HYPNOTIC IN DOSES AS LOW AS 0.25 MG. IN TWO STUDIES WHERE 0.25 MG OF TRIAZOLAM WAS ADMINISTERED (see Johnson review), NO NEGATIVE PERFORMANCE EFFECTS WERE SEEN THE MORNING AFTER ADMINISTRATION. THEREFORE, IF A SLEEP-INDUCING COMPOUND WERE TO BE FIELDED IMMEDIATELY, OUR EVALUATION INDICATES THAT TRIAZOLAM IN A DOSE OF 0.25 MG WOULD PROBABLY BE AN EFFECTIVE HYPNOTIC AND WOULD PROBABLY NOT PRODUCE SUBSTANTIAL PERFORMANCE DECREMENTS UPON AWAKENING. THE MOST IMPORTANT CAVEAT TO ACCOMPANY THIS EVALUATION IS THAT SERIOUS PERFORMANCE DEFICITS CAN BE EXPECTED DURING THE FIRST SIX HOURS AFTER DRUG ADMINISTRATION. THEREFORE, THE DRUG SHOULD ONLY BE USED WHEN THERE IS A REASONABLE EXPECTATION THAT NO ACTION WILL BE REQUIRED OF THOSE USING THE DRUG FOR A PERIOD OF AT LEAST SIX HOURS. IN MILITARY OPERATIONS, SUCH A SCENARIO IS PROBABLY ONLY TO BE FOUND IN LONG DISTANCE TRANSPORT OF TROOPS.

XIL TRIAZOLAM IS FAVORED OVER MIDAZOLAM MAINLY ON THE BASIS OF MIDAZOLAM'S LACK OF AVAILABILITY IN THIS COUNTRY. COMPARED WITH THE INTERMEDIATE HALF-LIFE COMPOUNDS, CLOBAZAM IS QUITE PROMISING, BUT IS ALSO NOT AVAILABLE IN THIS COUNTRY. TEMAZEPAM WAS USED SUCCESSFULLY BY BRITISH PILOTS DURING THE FALKLANDS CONFLICT TO ENABLE THE BEST USE OF IRREGULARLY SCHEDULED AND INFREQUENT SLEEP PERIODS UNDER UNCOMFORTABLE CONDITIONS.

WHILE THIS IS ALSO A PROMISING COMPOUND, TEMAZEPAM IS AVAILABLE WITHIN THIS COUNTRY ONLY IN 15 MG AND 30 MG DOSES. THE 30 MG DOSE APPEARS TO STRONG FOR MILITARY USE AND THE 15 MG DOSE MAY NOT BE AN EFFECTIVE HYPNOTIC. THE 20 MG DOSE AS USED IN EUROPE MAY BE THE OPTIMUM DOSE. IT ALSO APPEARS THAT THE PREPARATIONS AVAILABLE IN THIS COUNTRY MAY HAVE A SLOWER HYPNOTIC ONSET THAN THOSE AVAILABLE IN EUROPE AND THUS MAY BE LESS SUITED AS A MILITARY HYPNOTIC. NOTE THAT ALTHOUGH THESE DRUGS ARE CLASSIFIED AS INTERMEDIATE HYPNOTICS ON THE BASIS OF THEIR PLASMA CLEARANCE RATES, THEIR ONSET AND DURATION OF HYPNOTIC ACTION APPEARS ALONG WITH OXAZEPAM'S TO BE ABOUT EQUIVALENT TO TRIAZOLAM'S, AGAIN INDICATING THE DISSOCIATION BETWEEN PHARMACOLOGIC AND BEHAVIORAL PARAMETERS. AS WE LOOK AT THE LONG HALF LIFE BENZODIAZEPINES WE DO FIND THAT THEY ARE LESS DESIRABLE FOR MILITARY USE AS HYPNOTICS, ALTHOUGH DIAZEPAM HAS BEEN SHOWN IN SOME STUDIES TO PROVIDE HYPNOTIC EFFECTS RATHER QUICKLY.

XIII. WHILE REVIEW OF CURRENT LITERATURE INDICATES THAT TRIAZOLAM AT A DOSE OF 0.25 MG WOULD PROBABLY BE AN EFFICACIOUS AND SAFE HYPNOTIC, THERE ARE IMPORTANT QUESTIONS ABOUT ITS MILITARY USE WHICH HAVE NOT BEEN ADDRESSED IN THE CLINICAL LITERATURE. THESE QUESTIONS, WHICH SHOULD BE ANSWERED AS SOON AS POSSIBLE ARE:

(viewgraph 7)

A. WILL TRIAZOLAM AT 0.25 MG BE EFFECTIVE IN THE CONTEXT OF A RAPID DEPLOYMENT MISSION? SPECIFICALLY, WILL IT BE ABLE TO COUNTERACT THE FOLLOWING FACTORS WHICH ARE PRESENT IN THE MILITARY SITUATION, BUT NOT IN EXISTING CLINICAL STUDIES:

1. NOISY AND UNCOMFORTABLE PHYSICAL SURROUNDINGS

2. ADMINISTRATION AT A HIGH POINT IN THE CIRCADIAN RHYTHM.

3. ADMINISTRATION TO SUBJECTS WHO HAVE A HIGH LEVEL OF ANXIETY AND AUTONOMIC AROUSAL.

B. AT THE PEAK OF TRIAZOLAM'S ACTION, HOW EASILY CAN THE SUBJECT BE AROUSED AND WHAT DEFICITS WILL BE SEEN IN SOLDIER'S ABILITIES TO RESPOND TO AN EMERGENCY SUCH AS A CRASH LANDING OF THEIR PLANE? IN ONE STUDY, THERE WAS DIFFICULTY AROUSING SUBJECTS AFTER THE ADMINISTRATION OF 0.5 MG OF TRIAZOLAM. FURTHER, THE SLOWING EFFECTS OF BENZODIAZEPINES ON MOST TASKS MAKE THIS OF PARTICULAR CONCERN.

C. SINCE WE CAN NEVER BE SURE IN A MILITARY OPERATION THAT SOLDIERS WILL NOT BE REQUIRED TO BE AWAKENED FOR LAST MINUTE INSTRUCTIONS OR FOR OTHER TASKS, WE MUST ALSO ASK: AT THE PEAK OF TRIAZOLAM'S ACTION, WHAT IS THE NATURE AND

MAGNITUDE OF OTHER PERFORMANCE DEFICITS? OBVIOUSLY THE EFFECTS OF BENZODIAZEPINES ON MEMORY ARE QUITE IMPORTANT HERE.

D. WHAT ARE THE PERFORMANCE DEFICITS EXPERIENCED FOR 24 HOURS FOLLOWING TRIAZOLAM INDUCED SLEEP? CLINICAL STUDIES SUGGEST THAT THE PERFORMANCE DEFICITS WHICH TYPICALLY ACCOMPANY THE LOW POINTS OF THE CIRCADIAN RHYTHM ARE SIGNIFICANTLY ACCENTUATED FOLLOWING BENZODIAZEPINE INDUCED SLEEP. FURTHER, IT IS QUITE PROBABLE THAT SOLDIERS WILL BE REQUIRED TO PERFORM SIX HOURS AFTER TRIAZOLAM INGESTION. WHILE EXTRAPOLATION OF PLASMA CLEARANCE RATE AND BEHAVIORAL STUDIES INDICATES THAT FEW ADVERSE PERFORMANCE EFFECTS CAN BE EXPECTED AFTER SIX HOURS, MOST CLINICAL STUDIES HAVE USED SLEEP PERIODS IN EXCESS OF SIX HOURS SO LITTLE DIRECT DATA ON THAT QUESTION IS AVAILABLE.

XIV. A HIGH PRIORITY FOR THE DEPARTMENT'S RESEARCH PROGRAM IS A STUDY IN WHICH THE QUESTIONS LISTED ABOVE WOULD BE ANSWERED. BRIEFLY, THE STUDY WOULD LOOK AT:

(viewgraph 8)

A. THE EFFICACY OF 3 DOSES OF TRIAZOLAM, 0.125, 0.25, AND 0.5 MG, [illegible] FOLLOWING BENZODIAZEPINE ADMINISTRATION. TESTING WOULD INCLUDE MEMORY, REACTION TIME, AND TIMED MOTOR TASKS AS A MINIMUM.

XV. FOLLOW UP PROJECTS TO BE CONSIDERED INCLUDE:

(viewgraph 9)

A. FURTHER DEFINITION OF THE ACTIONS OF TRIAZOLAM, IN PART TO DETERMINE WHETHER THERE IS A NEED TO LOOK FOR A BETTER DRUG AND TO FURTHER SPECIFY CONDITIONS OF USE. SPECIFIC GOALS WOULD BE:

1. A CAREFUL DELINEATION OF POTENTIAL NEGATIVE EFFECTS. E.G. IF WE ALLOW SUFFICIENT TIME FOR MEMORY CONSOLIDATION BEFORE ALLOWING AN INDIVIDUAL TO

RETURN TO SLEEP, CAN THE MEMORY PROBLEMS ASSOCIATED WITH BENZODIAZEPINE USE BE AVOIDED?

2. DETAILED SPECIFICATION OF THE TIME COURSE OF BOTH POSITIVE AND NEGATIVE EFFECTS.

3. RELATIONSHIP OF PLASMA CLEARANCE RATES TO THE TIME COURSE OF BEHAVIORAL EFFECTS?

4. WHAT ARE THE INTERACTIONS WITH CHOLINERGICS AND ANTICONVULSANTS?

5. ADDITIONAL EXAMINATION OF DELAYED EFFECTS—E.G. REM REBOUND, DEPENDENCY ON THE DRUG FOR SUBSEQUENT SLEEP, PHASE SHIFTING OF SUBSEQUENT SLEEPS, DESYNCHRONIZATION OF SLEEP FROM OTHER BIORHYTHMS.

6. WHAT IS THE RANGE OF INDIVIDUAL VARIABILITY IN THE EFFECTS?

7. COMPARE THE NATURE AND RESTORATIVE POWER OF TRIAZOLAM-INDUCED SLEEP WITH NATURAL SLEEP.

B. IF TRIAZOLAM IS NOT THE PERFECT MILITARY SLEEP-INDUCER, RESEARCH SHOULD LOOK AT OTHER COMPOUNDS. THE FRENCH, MILITARY INCIDENTALLY ARE COMPARING THE BEHAVIORAL EFFECTS OF VARIOUS BENZODIAZEPINES HYPNOTICS USING A COMPUTERIZED ASSESSMENT BATTERY AFTER AROUSAL FROM BENZODIAZEPINE INDUCED SLEEP.

1. COMPARE WITH CLOBAZAM, NOT CURRENTLY AVAILABLE IN U.S., BUT LITERATURE INDICATES FEW IF ANY PERFORMANCE DEGRADING EFFECTS.

2. COMPARE WITH THE 20 MG DOSE OF TEMAZEPAM 20 MG. WHICH HAS BEEN SUCCESSFULLY USED IN EUROPE.

3. EXAMINATION OF THE QUESTION OF WHETHER OR NOT MULTIPLE BENZODIAZEPINE RECEPTOR SUBTYPES EXIST CORRESPONDING TO BEHAVIORAL EFFECTS. BEHAVIORAL ANALYSIS IS CRITICAL TO THIS QUESTION AND THE ANSWERS WILL GUIDE THE STRATEGY OF BENZODIAZEPINE DEVELOPMENT AND SELECTION.

4. COMPARE WITH OTHER BENZODIAZEPINES AND WITH NON-BENZODIAZEPINE COMPOUNDS SUCH AS DSIP, SUBSTANCE S, INTERLEUKIN-1.

5. CONSIDER THE POSSIBILITY OF DRUGS WHICH MIGHT ACT AS A

TRIGGER FOR NATURAL SLEEP AS OPPOSED TO THOSE WHICH INDUCE AND MAINTAIN A "DRUGGED" SLEEP.

(viewgraph 11)

C. INVESTIGATE THE USE OF COMPOUNDS TO AROUSE PERSONNEL FROM DRUG-INDUCED SLEEP IN ORDER TO PROVIDE QUICK AWAKENING WITHOUT HANGOVER EFFECTS. TRH, BENZODIAZEPINE ANTAGONISTS, AND GABA-RELATED COMPOUNDS ARE STARTING POINTS.

XVI. (summary) IN SUMMARY, (viewgraph 12)

A. IF A SLEEP INDUCING COMPOUND FOR RAPID DEPLOYMENT OPERATIONS IS REQUIRED IMMEDIATELY, WE WOULD RECOMMEND THE USE OF TRIAZOLAM, 0.25 MG.

B. INITIALLY, THE USE OF TRIAZOLAM SHOULD BE RESTRICTED TO INFREQUENT USE IN SITUATIONS IN WHICH SOLDIERS ARE NOT EXPECTED TO BE AWAKENED FOR SIX HOURS.

C. THE DEPARTMENT OF BEHAVIORAL BIOLOGY, WRAIR IS PLANNING A

STUDY TO EXAMINE THE EFFECTS OF VARIOUS DOSES OF TRIAZOLAM ON SUCH PARAMETERS AS:

1. THE INDUCTION AND MAINTENANCE OF SLEEP IN MILITARY USE.

2. THE ABILITIES OF SUBJECTS TO PERFORM BOTH COGNITIVE AND EMERGENCY SURVIVAL TASKS UPON BEING AWAKENED AT THE HIGH POINT OF TRIAZOLAM'S ACTIONS.

3. THE RESIDUAL EFFECTS OF TRIAZOLAM ON PERFORMANCE.

D. THE DEPARTMENT IS PLANNING ADDITIONAL STUDIES ON SLEEP INDUCING DRUGS TO INCLUDE:

1. MORE PRECISE AND MORE DETAILED SPECIFICATIONS OF THE ACTIONS OF TRIAZOLAM AND OTHER HYPNOTIC DRUGS.

2. COMPARISONS OF TRIAZOLAM WITH CLOBAZAM, TEMAZEPAM, AND OTHER COMPOUNDS.

3. RESEARCH INTO THE APPLICATION OF DRUGS WHICH CAN COUNTERACT THE EFFECTS OF HYPNOTIC DRUGS, QUICKLY AWAKENING THE SOLDIER AND LEAVING HIM WITH NO RESIDUAL PERFORMANCE DEFICITS.

WE THANK YOU FOR YOUR INTEREST AND ATTENTION TO THIS MATTER AND WE WOULD AT THIS POINT WELCOME FURTHER QUESTIONS AND DISCUSSION.

TO BE ELIGIBLE FOR IMMEDIATE FIELDING,

CANDIDATE DRUGS SHOULD BE:

CURRENTLY APPROVED FOR USE AS A HYPNOTIC IN THIS COUNTRY

COMMERCIALLY AVAILABLE IN AN APPROPRIATE ORAL UNIT DOSE

DRUGS AND DRUG CLASSES UNDER REVIEW

BENZODIAZEPINES

ANTI-HISTAMINES

BARBITURATES

CHLORAL HYDRATE AND CHLORAL BETAINE

NEUROPEPTIDES (E.G. DSIP, SUBSTANCE S)

ETHCHLORVYNOL

ETHINAMATE

REPRESENTATIVE BENZODIAZEPINES

I. SHORT HALF LIFE (< 5 HOURS)

TRIAZOLAM MIDAZOLAM

II. INTERMEDIATE HALF LIFE (5 TO 24 HOURS)

NITRAZEPAM FLUNITRAZEPAM CLOBAZAM* LORAZEPAM TEMAZEPAM
BROMAZEPAM ESTRAZOLAM ALPRAZOLAM OXAZEPAM LOPRAZOLAM
LORMETAZEPAM

III. LONG HALF (> 24 HOURS)

CHLORDIAZEPOXIDE DIAZEPAM FLURAZEPAM

*CLOBAZAM IS METABOLIZED LIKE A LONG HALF LIFE BENZODIAZEPINE, BUT ITS PHYSIOLOGICAL AND BEHAVIORAL EFFECTS ARE THOSE OF AN INTERMEDIATE HALF LIFE BENZODIAZEPINE

PROBLEMS ASSOCIATED WITH SOME HYPNOTICS

ANTI-HISTAMINES

PARADOXICAL AROUSING REACTION IN SOME SUBJECTS; SUBSTANTIAL POTENTIATION OF ANTICHOLINERGICS; UNCOMFORTABLE PHYSICAL EFFECTS.

BARBITURATES

HIGH ABUSE POTENTIAL; NEGATIVE PERFORMANCE EFFECTS FOLLOWING SLEEP; RELATIVELY HIGH POTENTIAL FOR ADVERSE PHYSICAL REACTIONS; SOME PRODUCE SUBSTANTIAL POTENTIATION OF ANTICHOLINERGICS; SOME HAVE UNUSUALLY WIDE VARIATIONS IN ABSORPTION FROM GASTROINTESTINAL TRACT

CHLORAL HYDRATE AND CHLORAL BETAINE

ABUSE POTENTIAL; POTENTIAL FOR ADVERSE PHYSICAL AND BEHAVIORAL EFFECTS INCLUDING SOMNAMBULISM; PARADOXICAL AROUSING REACTION IN SOME SUBJECTS.

ETHCHLORVYNOL

ABUSE POTENTIAL; SIGNIFICANT ADVERSE PERFORMANCE EFFECTS INCLUDING PRODUCTION OR AGGRAVATION OF DEPRESSION.

ETHINAMATE

RELATIVELY LITTLE DATA AVAILABLE; PARADOXICAL AROUSING REACTION IN SOME SUBJECTS; ADVERSE PHYSICAL EFFECTS.

NEUROPEPTIDES

NOT CURRENTLY AVAILABLE FOR USE IN THIS COUNTRY; RELATIVELY LITTLE HUMAN DATA;

DESIRED QUALITIES OF CANDIDATE BENZODIAZEPINES

EFFECTIVE HYPNOTIC (SLEEP-INDUCING) PROPERTIES

RAPID ONSET OF HYPNOTIC EFFECT

SHORT DURATION OF HYPNOTIC EFFECT (ABOUT SIX HOURS)

EASY AROUSAL FROM DRUG-INDUCED SLEEP

LACK OF NEGATIVE EFFECTS DURING PERIOD OF THE DRUG'S HYPNOTIC ACTION

LACK OF NEGATIVE EFFECTS AFTER THE PERIOD OF THE DRUG'S HYPNOTIC ACTION

LOW ABUSE POTENTIAL

	AVAILABLE IN U.S.	RAPID ONSET OF SLEEP	EASY AROUSAL	LOW ACUTE NEGATIVE EFFECTS	BRIEF DURATION	LOW RESIDUAL NEGATIVE EFFECTS	LOW ABUSI POTENTIAI
SHORT HALF LIFE (>5 hours)							
Triazolam	YES	YES	?	NO	YES	?	?
Midazolam	NO	YES	?	NO	YES	YES	?
INTERMEDIATE HALF LIFE (5-24 hours)							
Clobazam*	NO	YES	?	YES	YES	YES	?
Temazepam	YES	YES	YES	NO	YES	YES	?
Oxazepam	YES	YES	NO	NO	YES	?	?
Nitrazepam	NO	?	NO	?	NO	YES	?
LONG HALF LIFE (>24 hours)							
Chlordiazepoxide	YES	NO	NO	NO	NO	NO	NO
Diazepam	YES	YES	?	NO	NO	NO	NO

*Clobazam is metabolized like a long half life benzodiazepine, but its physiological and behavio properties resemble an intermediate half-life benzodiazepine.

CRITICAL QUESTIONS IN THE USE OF 0.25 MG TRIAZOLAM

I. WILL TRIAZOLAM BE ABLE TO COUNTERACT THE FOLLOWING FACTORS WHICH ARE PRESENT IN THE MILITARY SITUATION, BUT NOT IN EXISTING CLINICAL STUDIES:

   A. NOISY AND UNCOMFORTABLE PHYSICAL SURROUNDINGS

   B. ADMINISTRATION AT A HIGH POINT IN THE CIRCADIAN RHYTHM.

   C. ADMINISTRATION TO SUBJECTS WHO HAVE A HIGH LEVEL OF ANXIETY AND AUTONOMIC AROUSAL.

II. AT THE PEAK OF TRIAZOLAM'S ACTION, HOW EASILY CAN THE SUBJECT BE AROUSED AND WHAT DEFICITS WILL BE SEEN IN SOLDIER'S ABILITIES TO RESPOND TO AN EMERGENCY SUCH AS A CRASH LANDING OF THEIR PLANE?

III. AT THE PEAK OF TRIAZOLAM'S ACTION, WHAT IS THE NATURE AND MAGNITUDE OF OTHER PERFORMANCE DEFICITS?

IV. WHAT ARE THE PERFORMANCE DEFICITS EXPERIENCED FOR 24 HOURS FOLLOWING TRIAZOLAM INDUCED SLEEP?

THE EFFICACY OF 3 DOSES OF TRIAZOLAM, 0.125, 0.25, AND 0.5 MG, IN INDUCING SLEEP

IN SUBJECTS:

1. WHO ARE IN A BEHAVIORALLY AROUSED STATE
2. AND WHO ARE AT A CIRCADIAN HIGH POINT,
3. IN AN UNCOMFORTABLE AND NOISY ENVIRONMENT

SUBJECTS WOULD BE AWAKENED AND REQUIRED TO PERFORM A REALISTIC ESCAPE TASK AT THE HIGH POINT OF DRUG ACTION.

SUBJECTS WOULD ALSO BE TESTED ON TASKS WHICH HAVE BEEN SHOWN TO BE SENSITIVE TO BENZODIAZEPINES AT THE HIGH POINT OF DRUG ACTION, AND AT SIX THROUGH TWENTY-FOUR HOURS FOLLOWING BENZODIAZEPINE ADMINISTRATION.

FURTHER RESEARCH ON TRIAZOLAM

A. CAREFUL DELINEATION OF POTENTIAL NEGATIVE EFFECTS.

B. DETAILED SPECIFICATION OF THE TIME COURSE OF BOTH POSITIVE AND NEGATIVE EFFECTS.

C. RELATIONSHIP OF PLASMA CLEARANCE RATES TO THE TIME COURSE OF BEHAVIORAL EFFECTS.

D. WHAT ARE THE INTERACTIONS OF TRIAZOLAM WITH CHOLINERGICS AND ANTICONVULSANTS?

E. ADDITIONAL EXAMINATION OF DELAYED EFFECTS.

F. WHAT IS THE RANGE OF INDIVIDUAL VARIABILITY IN THE EFFECTS?

G. COMPARE THE NATURE AND RESTORATIVE POWER OF TRIAZOLAM-INDUCED SLEEP TO NATURAL SLEEP.

FUTURE RESEARCH ON OTHER HYPNOTICS

COMPARE WITH CLOBAZAM.

COMPARE WITH TEMAZEPAM 20 MG. DOSE.

EXAMINATION OF THE QUESTION OF WHETHER OR NOT MULTIPLE BENZODIAZEPINE RECEPTOR SUBTYPES EXIST, CORRESPONDING TO BEHAVIORAL EFFECTS.

COMPARE WITH OTHER BENZODIAZEPINES AND WITH NON-BENZODIAZEPINE COMPOUNDS SUCH AS DSIP, SUBSTANCE S, INTERLEUKIN-1.

CONSIDER THE POSSIBILITY OF DRUGS WHICH MIGHT ACT AS A TRIGGER FOR NATURAL SLEEP AS OPPOSED TO THOSE WHICH INDUCE AND MAINTAIN A "DRUGGED" SLEEP.

INVESTIGATE THE USE OF COMPOUNDS TO AROUSE PERSONNEL FROM DRUG-INDUCED SLEEP IN ORDER TO PROVIDE QUICK AWAKENING WITHOUT HANGOVER EFFECTS.

SUMMARY

*IF A SLEEP INDUCING COMPOUND FOR RAPID DEPLOYMENT OPERATIONS IS REQUIRED IMMEDIATELY, RECOMMEND THE USE OF TRIAZOLAM, 0.25 MG.

*INITIALLY, THE USE OF TRIAZOLAM SHOULD BE RESTRICTED TO INFREQUENT USE IN SITUATIONS IN WHICH SOLDIERS ARE NOT EXPECTED TO BE AWAKENED FOR SIX HOURS.

*THE DEPARTMENT OF BEHAVIORAL BIOLOGY, WRAIR IS PLANNING A STUDY TO EXAMINE THE EFFECTS OF VARIOUS DOSES OF TRIAZOLAM ON SUCH PARAMETERS AS:

'THE INDUCTION AND MAINTENANCE OF SLEEP IN MILITARY USE.

'THE ABILITIES OF SOLDIERS TO PERFORM BOTH COGNITIVE AND EMERGENCY SURVIVAL TASKS UPON BEING AWAKENED AT THE HIGH POINT OF TRIAZOLAM'S ACTIONS.

'THE RESIDUAL EFFECTS OF TRIAZOLAM ON PERFORMANCE.

*THE DEPARTMENT IS PLANNING ADDITIONAL STUDIES TO INCLUDE:

'MORE PRECISE AND MORE DETAILED SPECIFICATIONS OF THE ACTIONS OF TRIAZOLAM AND OTHER HYPNOTIC DRUGS.

'COMPARISONS OF TRIAZOLAM WITH CLOBAZAM, TEMAZEPAM, AND OTHER COMPOUNDS.

'RESEARCH INTO THE APPLICATION OF DRUGS WHICH CAN COUNTERACT THE EFFECTS OF HYPNOTIC DRUGS, QUICKLY AWAKENING THE SOLDIER AND LEAVING HIM WITH NO RESIDUAL PERFORMANCE DEFICITS.