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ADP011053

TITLE: Gold Standard Tests

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TITLE: Medication for Military Aircrew: Current Use, Issues, and Strategies for Expanded Options [les medicaments pour les equipaes militaires: Consommation actuelle, questions et strategies pour des options elargies]

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ADP011041 thru ADP011058

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Gold Standard Tests

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INTRODUCTION

While drug toxicity which targets internal, especially excretory, organs is aggressively evaluated in laboratory and clinical trials prior to marketing, adverse effects on systems of interest to aviation, e.g., the special senses, are only rarely evaluated. It is the intent of this guideline to recommend tests which have been successfully employed in earlier research to detect medication effects. Where that proved impossible, tests were chosen that were known to be sensitive in detecting abnormalities typically caused by medications (e.g., contrast sensitivity function for visual abnormalities). Also, tests with a history of use in clinical medicine were preferred, since they were more likely to be available, well validated, and familiar to potential investigators, although for some areas such as cognitive testing this was impractical. Since baseline testing should be readily available when investigating drug effects, tests with a higher degree of sensitivity and reproducibility were preferred to those with greater specificity. Note that some tests have been discussed, not necessarily to be recommended. Also, even for those tests that are recommended, we do not mean to imply that all tests be done on all drugs; the testing regimen should be tailored to potential areas of concern.

The following sections are arranged by physiologic category, consisting of cognitive functions, special senses, critical organs, and physiologic responses to environmental demands such as acceleration.

CNS ASSESSMENT

Before designing a test protocol, the first question to answer is the following one: is use of the drug intended to allow the subject to alleviate a physiological stress in a physiological way, i.e., in a way he would spontaneously adopt to cope with the situation, or is it to allow the subject to exceed the limits of human stamina and endurance for a certain period of time? For example, multiple layovers, extended duty time, jet-lag, or continuous or sustained operations will lead to a sleep debt and a performance decrease. The use of hypnotics or chronobiotics in that situation may allow aircrew to get some recovery sleep and thus maintain performance; the primary goal is to avoid residual effects of hypnotics after waking up. In contrast, the use of a psychostimulant to cope with sleep deprivation entails a totally different approach. If we want to alleviate the detrimental effect on performance of military operators in a particular situation, time appears to be the critical factor. How long does the drug act? Assessing the duration of the drug effect compared to placebo is not as simple as it may appear. Different physiological, psychophysiological and performance effects will not change at the same rate; furthermore, the changes are not linear, nor do they include a "steady state" plateau. This problem is multiplied by the number of tests which are used, each of the resulting curves having its own characteristics. Thus, determining the duration of effect will involve a degree of subjectivity on the

part of the scientific team, even if optimal testing has been thoroughly carried out.

Determining safe limits of use is even more complicated. One should first list the different mental functions the drug is able to modify and then choose a test which will offer the best scientific conditions of validity and fidelity. Other characteristics may be of importance, especially usability under laboratory or field conditions. The choice of the different mental abilities to be explored should ideally rely on a task analysis or on the knowledge of aircraft handling and complex system management. The job of military pilots is changing rapidly; higher mental abilities, such as task sharing, workload management, decision making, and mission planning, are now as necessary to the success of a mission as basic perceptive and psychomotor abilities. Psychology has not yet produced tests able to assess such higher cognitive functions. The use of simulators offers an option, even if it gives only global performance data. Although we tend to focus on evaluating a drug from a purely cognitive point of view, one should not forget mood and feelings, since detrimental effects on the affective domain may lead to a performance decrement or risk-taking behavior. Finally, a last point of interest should be mentioned. Deleterious effects induced by operational drugs must be put in the context of the likely use of the drug. Military operations produce intense strain on personnel, and the resulting stress reaction may partially compensate for some side effects that appear under laboratory conditions, a point that should be kept in mind before rejecting a candidate drug.

Assessment Methods

This section will list some of the recommended tests and parameters used to assess drug effects and side effects on the CNS during laboratory or field experiments.

Vigilance Assessment by EEG Methods

Continuous or ambulatory EEG is the best means to measure the level of cortical arousal during the subject's activities. Besides constituting the central component of nocturnal polysomnography, as well as daytime nap studies, EEG can also be used in the daytime to detect drowsiness.^{1,2}

Sleep Scoring: Rechtschaffen & Kales' manual is the reference routinely used for staging and scoring

sleep studies.³ For scoring micro arousals, which may appear during any sleep episode, an American Sleep Disorders Association (ASDA) task force has recommended guidelines.⁴ Micro sleeps, defined as an abrupt decrease in vigilance, have been described in the laboratory⁵ and during various field experiments. Detecting them in a military setting is of particular interest, as they may be responsible for a sudden decrease in performance. Established scoring rules do not exist for this type of event, but it is generally accepted that they present as a burst of 4 to 7 Hz rhythm for 1 to 10 seconds.⁶ In the French experience, especially with several studies on stimulants, a micro sleep was defined as a period of stage 1 or deeper sleep which occurred after a minimum of 15 seconds of wakefulness, and lasted between 3 and 14 seconds. After a first micro sleep, another period of wakefulness of at least 15 seconds was deemed necessary before one could score a second micro sleep. These rules are similar to those used to score micro arousals, although the situation is reversed. The defined duration is a compromise, since it seems difficult to score events which last less than 3 seconds, especially on a continuous recording; however, if different events with a cumulative duration of more than 3 seconds were documented during the same epoch, a single micro sleep was registered. A cumulative index of micro sleeps during a period of sustained sleep deprivation seems to be a valuable parameter to assess the power of a stimulant.⁷

Multiple Sleep Latency Testing/Maintenance of Wakefulness Testing: Designed by Carskado and Dement in 1977, multiple sleep latency testing (MSLT) is now widely used. The ASDA scoring rules offer a standard methodology.⁸ The maintenance of wakefulness test (MWT), first described by Mitler et al. in 1982,⁹ aims to assess the ability to remain awake under soporific circumstances. There is a relative lack of reference data in the general population, although recent progress was made by Doghramji et al.,¹⁰ who defined normative data with a lengthened duration of test. If these data are confirmed, it will be possible in the future to use MWT as a routine test. The use of combined MSLT and MWT is also possible using the MAST technique described by Erman et al.¹¹ It has been shown that the MWT has a higher discriminative power than the MSLT to assess the effect of psychostimulants in narcolepsy.¹² MWT will likely become the reference test for psychostimulants in the near future, but for hypnotics it seems preferable to continue using the standard MSLT.

Actigraphic Data

Many actigraphic devices are now available to evaluate physical activity. The main problem with actigraphic data lies in establishing a suitable method for processing the results. For drug studies, one method is to compare mean level of activity during defined periods under two pharmacological conditions, but there exists a feeling of dissatisfaction with this type of processing. In the future the dichotomy index, which aims to measure the contrast between wakefulness and sleep, may prove to be a valuable alternative;¹³ its calculation will probably be included in the software of actigraphic devices.

Subjective Data on Sleep Wake Rhythms

Visual Analogue Scales (VAS) are commonly used to measure the subject's own assessment of alertness and mood. Within the many scales available, one can choose the Bond and Lader VAS,¹⁴ the Stanford sleepiness scale,¹⁵ or the Epworth sleepiness scale. The last is more useful to evaluate sleepiness related to sleep disorders.¹⁶ The Bond and Lader VAS includes 16 dimensions which can be clustered into three major categories, consisting of vigilance, mood, and stress level. It has been used satisfactorily during sleep deprivation experiments, and also during field research investigating aircrew fatigue during multiple layovers.

Sleep logs are routinely used as well, as they provide valuable information on subjects' behavior.¹⁷ In the case of field research, the subject may be asked to write down additional information such as stimulant or medication consumption, hours of work and rest, and type of work, such as in flight or on the ground.

The Horne and Ostberg questionnaire is also used for the assessment of subjects' chronotype.¹⁸ It is useful to avoid the recruitment of extreme subjects, such as extreme "morning" and "evening" types, whose chronobiologic characteristics may impair the homogeneity of the studied population.

Mental Performance

The main test battery employed in military research laboratories is the AGARD STRES Battery, which was specifically developed to assess the effect of environmental stressors on mental performance.¹⁹ The STRES battery includes 7 different tests:

- Reaction times (simple and complex),
- Mathematical processing,

- Memory search,
- Spatial processing,
- Unstable tracking,
- Grammatical reasoning, and
- Dual task (unstable tracking with concurrent memory search).

172 scientific references about these different tests are available in the AGARDograph. The STRES battery has been used satisfactorily during numerous laboratory experiments performed by the French aeromedical centers, three of which are listed.^{2,20,21} The battery has also been implemented on desktop computers for field studies. However, these tests have become less standardized between countries than originally planned. Two main reasons may account for this. Firstly, some laboratories have forsaken the use of some tests to shorten their experimental protocols. Secondly, differences between computers, especially in terms of processor speed, may lead to unexpected variation between time or score measurements. This point is of particular interest in the case of collaborative studies.

Focused attentional performance may be assessed with the BATP test^{22,23,24} of the "Etablissement d'Application Psychotechnique," one of many tests available to assess attentional performance.^{25,26} The subject must detect targets embedded in distractors, the shapes of which are very similar. The test lasts 10 minutes, and puts significant strain on the subject. It has been widely used in a paper and pencil version during sleep deprivation experiments. Recently, a software version has been developed and validated.²⁷

VISUAL ASSESSMENT

Spectrum of Ophthalmic Toxicity of Systemic Drugs

Ocular toxicity from systemic medications may present in any of several ways. The following system follows a largely anatomic classification, with some examples of agents under each heading which are known to present in such a fashion.

1. Cornea – corneal deposits
 - amiodarone, antimalarials, indomethacin

2. Anterior chamber – autonomic effects
 - antihistamines, antihypertensives, innumerable other drugs
3. Lens – cataracts
 - allopurinol, clomiphene, sulfonamides
4. Retina – retinopathy/maculopathy
 - antimalarials, thioridazine, canthaxanthine, tamoxifen, niacin
5. Optic nerve – toxic optic neuropathy
 - ethambutol, chloramphenicol, lithium

Testing Visual Function

Baseline testing is crucial, since early ocular toxicity may manifest as a minor decrement in testing which at that point may still be within normal range. Furthermore the normal range of a healthy population is not well established for all tests, and baseline testing also allows one to identify minor preexisting abnormalities which might otherwise be blamed on the drug. Since ocular toxicity may not manifest equally in each eye, tests should be administered in a monocular fashion.

Corneal and lenticular opacities are relatively rare, and usually readily identifiable by standard biomicroscopy. Visual blurring due to autonomic drug effects is very common, but because it is readily reversible, there has been little effort devoted to evaluating screening tests. However, testing for high and low contrast visual acuity should readily identify drug toxicity presenting in this fashion.

For a number of reasons, considerably more effort has been expended on screening tests for drug-induced retinopathy, particularly that due to antimalarials. The changes may not be reversible and may even progress off therapy. Also, retinal changes may not be visible until permanent damage has occurred. Furthermore, some patients with established retinopathy are asymptomatic. However, despite the large body of research, the literature is confusing and controversial.¹ This may be due in large part to a lack of agreement as to what defines the earliest stages of retinopathy, and also to a lack of studies which have followed patients over the long term. Goldman perimetry², Amsler grid testing³, electroretinography⁴, and electro-oculography⁵ have all been evaluated as screening tests for early chloroquine retinal toxicity,

but results have been inconsistent. In many cases, the results have correlated well with established retinopathy, but less well with what was felt to represent early retinopathy. As noted earlier, this may be due to a lack of criteria for what actually constitutes early retinopathy, and to the practical and ethical dilemma of following patients over the long term to determine whether definite retinopathy actually developed.

Literature concerning toxic optic neuropathies is more limited, consisting largely of clinical findings noted in established cases. Definite cases of ethambutol optic neuropathy have displayed symmetric, central scotomata. Acquired color vision deficit has been a consistent finding, particularly a green weakness.⁶ Joubert et al showed significant deutan errors in patients on ethambutol early in the course of treatment, while tritan errors appeared later, in those who had been on the drug for more than two months⁷.

Defective color vision overlaps several of the earlier categories, particularly retinopathy and optic neuropathy. Many drugs are known to affect color vision (see Table 1, from WG-24). Probably because dyschromatopsia is defined by the results of functional testing, there is general agreement about optimal testing procedures. The Farnsworth-Munsell 100 Hue (FM-100) test has been used successfully to screen for solvent exposure⁸, and digoxin toxicity⁹, both revealing a dose-response relationship. In the former study, the Lanthony D-15 desaturated panel appeared to be a useful field screening tool, but did not provide as detailed an assessment as the FM-100. The prevalence of blue-yellow deficiencies by FM-100 in patients on phenytoin and carbamazepine correlated well with the presence of neurotoxicity;¹⁰ tritan screening plates also identified dyschromatopsics, but this was to be expected, since deficiencies in this study were confined to the blue-yellow axis (Type III).

Besides color vision, a number of vision tests depend on the integration of multiple ocular functions, but contrast sensitivity function (CSF) testing is particularly sensitive to a large number of abnormalities, including neuropathy, retinopathy, amblyopia, and glaucoma, as well as any abnormality affecting standard high contrast acuity.¹¹ Perhaps because of this broad sensitivity and lack of specificity, CSF testing has not been commonly employed in screening for drug-induced retinopathy or neuropathy. However, for evaluating drug effects over the short term in a relatively healthy

population, this lack of specificity should pose little problem. CSF testing has been shown to be sensitive to blood alcohol level in a dose related fashion (average level .09%), whereas perceived intoxication did not correlate to blood level.¹² CSF testing has also been shown to be enhanced by dopaminergic drugs.¹³

Given the increasing reliance on nighttime military operations, the effect of a drug on night vision is of obvious interest. No standardized test exists to evaluate visual acuity under scotopic conditions. There are standardized tests for evaluating contrast under low mesopic conditions, using instruments such as the Mesoptometer or the Nyktometer, but these tests evaluate a limited range of contrast levels, and to our knowledge neither instrument has been used to test for drug effects. It is possible to identify deficiencies in dark adaptation, by bleaching out rhodopsin under bright light, and then measuring the return of gross scotopic vision under dark conditions. This is a cumbersome test of doubtful sensitivity, and will not identify short term alterations; as an example, it has been used in cases of vitamin A malabsorption, where rhodopsin levels have become seriously depressed over a long period of time. Despite the fact that there appears to be a lack of validated testing techniques for scotopic vision, such a deficiency is of questionable significance in the area of drug testing, since the group is not aware of any drug which is thought to degrade scotopic vision in the absence of frank retinopathy or other structural disease.

Degradation of visual acuity with night vision goggles (NVG) is a distinctly separate issue, since NVGs involve low photopic rather than scotopic vision; the fact that the screen itself is green is evidence of that. The present generation of NVGs contain a phosphor screen which emits light of a defined wavelength, or narrow band of wavelengths, in the green spectrum, with the resulting low contrast image formed by varying intensities of green light. One would suspect that deficits in CSF testing might correlate with NVG acuity, and recent results have indeed demonstrated such a correlation, albeit not a strong one.¹⁴ It is possible to test NVG acuity directly. As long as illumination levels are strictly controlled, and the identical NVG device is used, results have been reproducible, but the amount of shift that would constitute a significant change would vary depending on the device and conditions.

Recommended Visual Function Tests

The following tests are recommended for evaluating ocular effects of therapeutic drugs in aviators.

Visual Acuity: High contrast visual acuity, far and near, using standard methods such as Snellen or Bailey-Lovie charts, performed at baseline, 3 days, and 6-12 months. A decrement of two lines on the Snellen chart is considered a significant change from baseline.

Ophthalmoscopy: Biomicroscopy with indirect ophthalmoscopy to evaluate for corneal deposits, cataracts and fundus changes, performed at baseline, and at 6-12 months. Any such findings are potentially significant.

FM-100: Standard saturated 85 chip panel, under 6750° K light source, performed at baseline and at 6-12 months. A difference in square roots of Total Error Scores exceeding 2.274 is considered to be a significant change.

Contrast Sensitivity Function Testing: Less available data, but other tests for screening visual function appear to sacrifice sensitivity for specificity. While Vistech or Pelli-Robson charts are simpler to administer, they measure larger incremental changes (0.12 log units) in CSF when compared with cathode ray tube-based tests. CSF testing should be performed at baseline, 3 days, and 6-12 months. A decrement of 0.05 log units is considered a significant change.

VESTIBULAR ASSESSMENT

In general, the vestibular system is part of the human equilibrium system. Information about position and movement is obtained by the vestibular, the visual and the somatosensory systems. Each of these systems covers a particular range in the frequency spectrum. In case of damage to, for instance, a semicircular canal system, compensation takes place within the central vestibular system itself. But it is also observed that in these cases patients rely much more on vision and on somatosensory information. In case of a bilateral loss, such as may occur due to gentamicin toxicity, one may observe a much stronger response from the other sensory systems. This has even lead to discussions about whether the vestibular system still has a vital function, or merely fine-tunes equilibrium; such a misinterpretation probably

occurs because of a lack of awareness that loss of other systems may elicit equally strong responses. When monitoring subjects for vestibular function, one has to be very careful to ensure that the system purportedly being examined is truly being evaluated.

When monitoring vestibular functioning, several important issues need to be understood.

Anamnesis: Because damage to the vestibular system due to drugs usually affects both labyrinths, the most important tool in standard diagnostic practice, the anamnesis, falls short. In the usual clinical situation, a vestibular deficit is suspected if a subject complains about vertigo, and a “quick and dirty” examination of eye movements shows spontaneous nystagmus, indicating a unilateral vestibular hypofunction. With a bilateral decrease of vestibular function, however, there is no spontaneous nystagmus and no vertigo is reported. The patient may be unsteady, but since he/she is often already in the hospital because of underlying illness, this finding is often misinterpreted even by trained otolaryngologists. (As an example, because patients treated with gentamicin were monitored with audiograms showing no decrease in function, and because the patients did not report vertigo and no spontaneous nystagmus was observed, the gradual decrease of vestibular function was often completely missed until the loss was complete.)

Reproducibility: If vestibular tests are carried out, they should take place on the same part of the day, in a reproducible manner, preferably by the same examiner, and a high level of arousal should be maintained during all examinations. It is known that test results may be influenced by the instructions before the test, and by whether the subject is kept busy during the test, for instance by performing mental arithmetic. In tests of the vestibulo-ocular reflex, the subject should be examined with the eyes open in a completely dark room; eyes closed versus eyes open in darkness may lead to different results. As another example, in case caloric irrigation is used, this should always be done with the same temperatures and with the same medium, not for instance alternately with water and air. Although this seems obvious, if examinations are done in different laboratories, the results may be difficult to compare because of these discrepancies.

Data Analysis: Because it is not always clear what sort of function deterioration might happen, it is advisable not to rely only on automatic data analyzing programs, but to also perform direct visual inspection of the data.

Tests for the Vestibulo-Ocular Reflex

Caloric Irrigation: Irrigation of both ears with water of 30 and 44 degree Celsius is the standard laboratory technique to assess a difference in function between the left and the right labyrinth. The test requires consistent laboratory practice because there are many factors which may influence the final result. A disadvantage of the test is poor patient acceptance, because nausea is easily provoked, and thus the test is not a good candidate to routinely monitor vestibular function. However, in order to assess vestibular function prior to a particular trial the caloric test may be quite useful.

Rotating Chair: A sudden stop from constant velocity yaw rotation with 90 degrees about the vertical axis results in a vestibular nystagmus, which disappears gradually. There are several characteristics which can be determined from this nystagmus response. The response can be described by an amplitude A and a time constant T (as a first order approach, neglecting the phase 2 response where the nystagmus reverses its direction). The test is not nauseating for the subject, but the inter- and intra-individual variability is great, demanding consistent test performance if any conclusions about decrease of vestibular function are to be drawn with sufficient certainty. This test is useful for monitoring vestibular functioning.

Although the time constants for pitch and roll rotation are different from the one obtained by yaw rotation, there is no indication that pitch and roll rotation should be monitored as well. Moreover, this requires special test devices to keep the head in the center of rotation during rotation about the vertical axis, and even more complex devices when other axes than the vertical axis are considered for rotation. As with pitch and roll, there is no indication that using other axes would give more useful information than that obtained by yaw rotation about the vertical axis alone; furthermore, rotation about other axes is rather provocative in terms of motion sickness.

Sinusoidal rotation at different frequencies is also useful, but it does not add more to the test results

obtained with the sudden stop test, with one exception; if visual suppression of vestibular nystagmus is examined, sinusoidal rotation provides a better evaluation than either sudden stop tests or caloric examination. (In fact, examining fixation suppression during caloric nystagmus should not be done at all; one loses the information from the vestibular nystagmus that has to be suppressed at that particular moment, hampering the computation of the suppression coefficient. This coefficient is the quotient from the nystagmus slow component velocity during fixation and the nystagmus slow component velocity without fixation. A coefficient exceeding 0.1 is usually judged as abnormal.)

For bedside testing Frenzel glasses can be used, the head being rotated to and fro by the patient him/herself. One has to be careful here, because the cervico-ocular reflex adds to the response. For instance, patients with a bilateral loss of vestibular function, a likely pattern with drug toxicity, may show an enhanced cervico-ocular reflex, which means that the resulting nystagmus pattern is hardly different from the one in healthy subjects. The same applies for stepping in place, rotating, because then the somatosensory information from the stepping itself is much more pronounced in these patients and may hamper the proper interpretation of the eye movements.

Tilt Chair: In order to look at ocular torsion of otolithic origin, subjects are tilted over angles up to some 60 degrees. Here again, strict adherence to testing technique is crucial, the more so since the response is in general rather small, with static eye torsion angles of 6-8 degrees being common. The within-subject variability is large. Preventing torsion of the recording device with respect to the head requires much attention, because that can easily account already for 2 or 3 degrees of torsion if not fixed appropriately. The otolith information is corroborated by the somatosensory information from pressure on the body, which also contributes to the eye torsion. Some experimenters try to avoid the cumbersome tilting of the whole body, by requiring the subject to only tilt his head; however, then the neck contributes to the torsion as well. The fact that one necessarily deals here with different sensory systems makes the interpretation of this test very difficult, to say the least. Although subjects find the tests easy to perform, this test doesn't seem to be appropriate for monitoring vestibular function.

Examining the subjective vertical is good in dealing with a unilateral vestibular deficiency, but in case a

bilateral loss is suspected, the subjective vertical is not affected, although the accuracy in the settings decreases.

Tests for Postural Control

(Sharpened) Romberg Test The advantage of measuring and comparing postural stability, with the subject standing with the eyes open and closed, is that it is a physiologic test situation. From the sway pattern a measure of stability can be derived, demonstrating whether standing was easy or required much energy. It is not necessary to measure EMG; with the available force measuring platforms, head trackers, or video equipment, one is readily able to record postural sway. When the system is put under pressure, for instance by having subjects standing on a layer of foam rubber and/or with the head in extension, everyone must put some effort into the process in order to stay upright. One should realize, however, that in all these posture tests training effects can be seen, not only during a single session, but also over several days. Nevertheless, the difficulty of the test can be adjusted to each individual subject, and the test is not provocative. If the precautions about standardization are taken into consideration, this test is a good candidate for monitoring the equilibrium function.

A simplified version of this test is the sharpened Romberg test; with the subject standing with the feet in tandem position, the number of side steps necessary to prevent falling during a trial of one minute is taken as a measure of stability. Although severe disturbances are easily recognized this way, it is also possible to minimize the number of side steps by trying hard to remain upright. This is not reflected in the number of side steps, making this test unreliable for monitoring purposes.

Modern tests on postural control vary the visual surroundings, apart or in combination with tilt of the platform on which the subject is standing. Although these rather complex tests throw some light on the subject's equilibrium system, the interpretation of the test results requires a lot of experience. It definitely elucidates how the subject uses sensory information, but it should be realized that the system in case of some disturbance always prefers to rely on the visual information first; apparently that is the easiest way to handle the situation. It is not immediately obvious that these tests provide more information on the equilibrium

system than the Romberg test with additional foam rubber.

Stepping Around: In normal daily life activities such as walking, information of all sensory systems is available and integrated to guarantee optimal postural control and a unique spatial orientation. In fact, analysis of the normal postural and gait activities gives the best impression of the functioning of the equilibrium system. For detailed analysis of the functioning of the different subsystems involved, complex apparatus is required. Generally, the tests are not demanding for the subjects, but the analysis of the data is quite demanding for the examiner. These tests could be indicative of diminished vestibular activity, and are very valuable to follow-up compensation processes for damage to a subsystem. They have proven their value for showing functional compensation by the other subsystems. For instance, the somatosensory contribution to the nystagmus during stepping in circles depends on the contribution of the semicircular canals; the bigger the lesions, the higher the gain of the somatosensory nystagmus slow component velocity. Although these tests perfectly reflect normal daily life situations, technical problems prevented widespread application. Today technical progress has allowed further elaboration of these tests. There is increasing interest primarily because of the increasing applications of virtual reality, but also for diagnostic purposes.

Central Vestibular Function Testing: Optokinetic nystagmus, pursuit and different types of spontaneous or provocative nystagmus are easily recorded, but do not reflect a bilateral decrease in vestibular function.

Coriolis-effects as a Sign of Vestibular Function: The simplest way to establish the presence of vestibular function is to have a subject, during constant velocity rotation with the eyes closed, tilt his head toward his shoulder. If the sensation perceived is one of tilting the head to the shoulder, the chance that vestibular areflexia is present is rather high. If this can be done with velocities up to 135 or 180 degrees/sec without any problems, the conclusion is straightforward, and no vestibular function is present. If the vestibular system is still intact, the effect of tilting the head during rotation with the eyes closed is rather disturbing to the subject; he/she feels as if falling over with the chair, and often nausea develops immediately. The Coriolis Stress Test using this paradigm to

determine how many head movements can be sustained by the subject without vomiting is, for obvious reasons, not useful for monitoring vestibular function on a regular basis.

CARDIOVASCULAR ASSESSMENT

Spectrum Of Cardiac Toxicity Of Systemic Drugs

Only a few of the many potential cardiotoxins, specifically certain of the antineoplastic agents, mood-altering drugs, anti-infective agents, antihypertensive drugs, and vaccines, have been shown to result in clinical heart disease. These drugs may have a direct toxic effect on the myocardium or the coronary vasculature, or they may disturb primarily the functions of impulse formation and conduction. Others affect the heart indirectly by altering autonomic regulation. In the case of those drugs that exert a direct toxic myocardial effect, the extent of damage tends to reflect the intensity and duration of exposure.

In addition to those agents that evince toxicity, there are also drugs that have the potential to induce a generalized hypersensitivity reaction. The heart may become a target organ during such reactions, and may suffer significant inflammatory injury.

Cardiovascular Manifestations of Adverse Reactions to Drugs

ECG Changes: Electrocardiographic changes induced by drugs may include ST-segment depression, prolongation of P-R interval, prolongation of the Q-T interval, T-wave inversion, appearance of U waves or increased U-wave amplitude. Examples of drugs which have been clearly documented to induce ECG changes include the antiparasitic drugs emetine, used in the treatment of amebiasis and schistosomiasis, and chloroquine used in the prophylaxis and treatment of several parasitic diseases, as well as psychotropic drugs, especially phenothiazines and tricyclic antidepressants.

Of the ECG changes noted earlier, the one receiving the most attention has been the QT interval, since drug-induced lengthening of cardiac depolarization has been to blame for a number of deaths.

Cardiac Rhythm Disturbances: These include extrasystoles, both supraventricular and ventricular, and tachycardias, both supraventricular and

ventricular, bradycardias, either sinus or due to A-V block. Ventricular arrhythmias can be caused from ventricular irritability due to direct effect of the drug on the myocardium, or due to prolongation of the Q-T interval noted above. Examples include antiparasitic agents, psychotropic drugs, antibiotics such as erythromycin, terfenadine, thyroid hormone, sympathomimetics, and anticholinesterases.

Cardiomyopathy: Cardiomyopathy can arise from direct damage of the myocardium by the drug, such as with antineoplastic drugs, emetine, phenothiazines, lithium, or sympathomimetics, or due to hypersensitivity reactions, which have been documented with antibiotics and vaccines.

Pericarditis: Certain drugs, such as emetine and methysergide, may induce pericarditis, either in conjunction with underlying myocarditis, or as a manifestation of mesothelial damage, in which case it may be associated with other manifestations such as peritonitis.

Alterations in Blood Pressure: Drugs may affect the heart indirectly through altering blood pressure, causing either hypotension such as with antihypertensive drugs, or hypertension, such as with oral contraceptives or sympathomimetics.

Recommended Cardiovascular Function Tests: To evaluate potential cardiotoxicity, the following tests are recommended. To be able to delineate effects which are actually induced by medication, testing is advisable prior to initiation of the drug.

ECG: A resting baseline ECG must be done to identify pre-existing abnormalities. Specifically, careful measurement of the Q-T interval must be done. This interval, measured from the beginning of the QRS to the end of the T wave, indicates the approximate total duration of ventricular systole. It varies with heart rate, sex and age; several formulae have been used to take these variables into account and provide a "corrected" Q-T measurement (Q-Tc). Certain drugs are known to cause Q-T prolongation, a list which seems to get longer by the month. A prolonged Q-T means that there is delayed repolarization of the ventricular myocardium, and this is associated with an increased predisposition to reentry phenomena, thus favoring the development of serious ventricular tachyarrhythmias, syncope, and sudden death. Even when corrected for heart rate (Q-Tc), this measurement displays considerable spontaneous

variation. When evaluating for drug-induced prolongation, one should obtain three tracings before instituting drug treatment, and three tracings after reaching a steady state. An average change in Q-Tc of greater than or equal to 35 msec is considered to be a significant difference, and unlikely to be due to chance.¹

Holter 24-Hour Rhythm Monitoring: Holter monitoring allows one to detect changes in rhythm conduction, as well as changes in heart rate variability, which serves as an index of autonomic nervous system function. Asymptomatic episodes of sinus bradycardia (with the heart rate as low as 30 beats per minute), sinus pauses of up to 3 seconds, and Möbitz type I second degree atrioventricular nodal (Wenckebach) block should be considered to be normal variants.²

Echocardiography: This is the premier diagnostic tool for the early diagnosis of cardiomyopathy and pericarditis caused by drugs.

Exercise Testing: This may be performed periodically in aviators to assess exercise capacity and to evaluate for coronary disease. It could be used to screen for adverse effects of drugs on exercise capacity, the blood pressure response to exercise, and/or provocation of arrhythmias. Maximal exercise capacity in normal individuals is influenced by familiarization with the test equipment, the level of training, and ambient conditions during the testing. When estimating functional capacity, the amount of work performed (or exercise stage achieved) should be measured, rather than the minutes spent exercising. Hypotension following exercise, defined as a drop in systolic pressure below the standing level pre-exercise, occurs in normals with an incidence of 1.9%, and may be symptomatic. Hypotension occurring late in exercise, or during the recovery phase, can be due to medications.³ Effort-induced supraventricular or ventricular arrhythmias may develop during exercise testing in normals, and may be symptomatic.⁴ The possibility of false-positive results must be considered if exercise testing is performed as part of drug testing.

Tilt table testing: Head-up tilt table testing can be used to screen for abnormal blood pressure or heart rate responses during treatment with medications. When the test is performed in the absence of provocative pharmacologic agents, it appears to discriminate between symptomatic patients and asymptomatic control subjects; the specificity of the

test when performed at angles of 60 -70° is about 90%, with a relatively low false-positive rate in the population tested.^{5,6,7}

PULMONARY ASSESSMENT

For certain classes of pharmacotherapeutic agents, pulmonary function assessment should be included as part of a comprehensive aeromedical assessment. In particular, for drugs that may affect airway function or the pulmonary interstitium, appropriate pulmonary function testing should be included.

Table 2 lists possible adverse pulmonary reactions of drugs with potential application in the aerospace environment. (derived from the Medical Letter 32, 827; Current Medical Diagnosis and Treatment 39th edition 2000).

Many other therapeutic agents besides those listed may have adverse pulmonary effects, and adverse effects may emerge in new medications observed over time. When considering the introduction of a new medication for aircrew, the possibility of a known or unknown adverse effect on pulmonary function should always be considered.

Aeromedical Concerns Related to Pulmonary Dysfunction

The primary aeromedical concerns with respect to pulmonary dysfunction include:

- aggravation of hypoxia
- compromise of G – tolerance
- possible pulmonary barotrauma

Hypoxia is a ubiquitous threat in aviation. Pulmonary dysfunction may aggravate hypobaric hypoxia by creating ventilation-perfusion mismatch through either small airways dysfunction, or by affecting regional lung compliance through inflammation, edema, fibrosis, or emphysema. Mild degrees of arterial desaturation, e.g., 90%, may occur in individuals with perfectly healthy lungs at moderate altitudes (e.g., 9,000–10,000 feet), reflecting alveolar oxygen tensions on the cusp of the oxyhemoglobin dissociation curve. In such circumstances, even moderate degrees of pulmonary dysfunction may result in significant further desaturation converting a tolerable degree of mild hypoxia to significant desaturation with resulting performance decrements.

While G-tolerance is primarily based on systemic perfusion, desaturation caused by G-related ventilation-perfusion mismatch may play a contributory role in G-endpoints. Because it is the least structurally supported organ, the distortable elastic lung may well represent the eventual limiting factor in man's tolerance to radial accelerative forces. In this setting, small airways disease and interstitial lung disease may play a significant role in G-tolerance and in creating the substrate for acceleration atelectasis.

Pulmonary barotrauma is an unlikely event, but may occur with explosive or rapid decompression in the presence of trapped gas, as with agents that have the potential to cause an asthmatic reaction.

Pulmonary Function Assessment of Drugs for Use in Aircrew

Since pulmonary function testing is a specialized evaluation requiring trained technicians and carefully calibrated equipment, testing for an aeromedical pharmacotherapeutic assessment should be carried out in an accredited pulmonary function laboratory with appropriate quality control. Specific technical details will not be addressed in this monograph.

Pulmonary function assessment of pharmacotherapeutic agents being assessed for use in aircrew should consider assessment of:

1. airways function,
2. lung volumes, and
3. diffusing capacity.

Assessment of Airway Function

Small airways caliber is affected by mechanisms including neural pathways, humoral control, direct physical and chemical effects, and local cellular mechanisms. Assessment of airway function should be included in the aeromedical assessment of any pharmacotherapeutic agent that may affect the autonomic nervous system (parasympathetic or sympathetic), or that may affect the release of vasoactive polypeptides which modulate nitric oxide production.

The following tests comprise a basic assessment of airway function.

- Forced expiratory volumes

- Flow-volume curves including low gas density spirometry

Additional tests may be added depending on the potential side-effects of the pharmacotherapeutic agent:

- low gas density spirometry
- tests of airway reactivity
 - before and after bronchodilator
 - bronchial provocation tests
- other specialized tests
 - single-breath nitrogen washout
 - frequency dependence of compliance

Forced Expiratory Volume (forced vital capacity volume-time analysis): From a forced vital capacity (FVC) maneuver, the volume expired in a given time during the forced vital capacity is measured and a plot derived of expired volume against time. Primary derivatives including the FVC (forced vital capacity) and FEV_1 (volume expired in 1 second) are recorded, as well as secondary derivatives including the FEV_1/FVC ratio and FEF_{25-75} , (average flow rate during the middle half of the FVC).

Airways obstruction due to inflammation, broncho-spasm, or loss of elastic support (emphysema) result in decreased values for FEV_1 , and the FEV_1/FVC ratio. However, these parameters may remain relatively well preserved in early small airways disease, and the sensitivity of the FEV_1 and the FEV_1/FVC ratio in detecting early small airways disease is low. On the other hand, a decrease in the ratio below 75% has a relatively high specificity for identifying airways disease, either reversible (as in asthma) or fixed (as in emphysema).

Flow-Volume Curves: Expiratory flow rates are plotted against expired volume change during an FVC. Both inspired and expired flow rates are plotted. Parameters measured include peak inspiratory (PIFR) and expiratory (PEFR) flow rates, and flow rates when 50% (FEF_{50}) and 75% (FEF_{75}) of the vital capacity have been expired.

The shape of the maximum expiratory flow-volume (MEFV) curve from about the last 75% of the FVC down to RV is largely effort independent, and is determined by the elastic recoil properties of the lung and the flow-resistive properties of the small

airways (<2mm). In healthy subjects, this segment is generally linear, but in subjects with small airways disease (e.g., asthma) or loss of elastic recoil (e.g., emphysema), the shape of this segment is “scooped” with a decrease in FEF_{50} and FEF_{75} .

Low Gas Density Spirometry: Flow volume curves are obtained with the subject breathing air, and then repeated after breathing a low gas density mixture of 80% helium and 20% oxygen. The resultant curves are superimposed by matching at RV. The difference in flow rates on helium versus air at 50% vital capacity ($V_{max\ 50}$) is measured, as is the volume at which expiratory flows converge (VisoV). The basis for this test is that turbulent flow in the larger central airways is density dependent, while flow in small airways (<2mm) is laminar and density independent. In normal lungs, small airways contribute only about 20% to total expiratory flow resistance, and so breathing gas of low gas density produces a significant increase (>20%) in $V_{max\ 50}$ by improving flow in large airways; since the curves converge late, VisoV is normally 10-20% of the FVC. In individuals with small airways disease or dysfunction, small airways contribute a much larger share to total airflow resistance, and when such individuals breathe low density gas, there is little or no (<20%) change in $V_{max\ 50}$, and VisoV is increased.

Specialized Tests of Small Airway Function: Other specialized tests used to assess small airways function include the single-breath nitrogen washout curve (Fowler’s test), and the frequency-dependence of compliance. These tests are generally available in research laboratories but not in routine clinical pulmonary function laboratories.

Sensitivity/Specificity of Tests of Small Airways Disease: The sensitivity and specificity of various pulmonary function markers of small airway function have been assessed and correlated with histopathologic findings in a number of studies. Low gas density spirometry and the single-breath nitrogen washout curve (closing capacity and slope of phase III) appear to provide the highest sensitivity. FEF_{50} and the MMFR show changes earlier than the FEV_1 or the FEV_1/FVC ratio, but are less sensitive than the earlier tests. All suffer from a problem with interindividual variability, which makes their clinical utility small. They do appear to be reasonably reproducible in a given individual.

Assessment of Airway Reactivity:

Before and After Bronchodilator: Assessment of FVC and expiratory flow rates at baseline and after administration of a beta-adrenergic bronchodilator such as salbutamol (albuterol) may demonstrate reversible airflow obstruction suggestive of asthma or reactive airways disease. An increase of 15% or greater in FEV₁ is indicative of reversible airways obstruction, but changes in other parameters including FEF₅₀, FEF₂₅₋₇₅, or specific airways resistance may also be suggestive.

Bronchial Provocation Testing (BPT): BPT is used to objectively assess airway reactivity. Various challenges may be used; the most commonly used and best standardized is the methacholine challenge test. After obtaining a best effort baseline FEV₁, subjects breathe increasing doses of nebulized methacholine with repeat FEV₁ determinations after each dose. The test is terminated when a 20% fall in FEV₁ compared with baseline has been achieved. The methacholine dose at which this occurs may be expressed as the cumulative dose (PD₂₀) or concentration (PC₂₀).

Measurement of Lung Volumes

Lung volumes may be affected by agents and diseases which cause

1. interstitial changes – e.g., edema, pneumonitis or fibrosis
2. loss of elastic recoil – e.g., emphysema
3. gas trapping – e.g., asthma, emphysema

Interstitial changes generally result in *decreased* lung volumes (restrictive lung disease), while loss of elastic recoil and gas trapping are reflected in *increased* lung volumes (obstructive lung disease).

Lung volumes are measured by

- gas equilibration techniques such as nitrogen washout (open circuit system breathing oxygen) or helium (closed circuit), or by
- body plethysmography, which calculates total thoracic gas (VTG) based on volume or pressure changes using Boyle's law.

The gas equilibration techniques measure only the volume of those areas in the lung in ventilatory communication with inspired gas, while the body plethysmograph measures the total volume of intrathoracic gas. By comparing lung volumes

measured by both methods, an estimate can be derived of gas trapping by comparing the functional residual capacity (FRC) from plethysmography with the gas equilibration technique. $FRC_{\text{box}}/FRC_{\text{gas}}$ may be used as an index of gas trapping, with values greater than one suggesting gas trapping.

Diffusion Tests

The carbon monoxide diffusing capacity (D_{LCO} or D_{CO}), also known as transfer factor, measures the transfer of a diffusion-limited gas (CO) across the alveolocapillary membrane. Carbon monoxide combines with hemoglobin about 210 times more readily than oxygen. In the presence of normal ventilatory function, and normal amounts of hemoglobin, the primary factor limiting diffusion is the alveolocapillary membrane. Diffusing capacity is essentially a measure of conductance of CO across that membrane. The D_{LCO} is reported in milliliters of CO per minute traversing the alveolocapillary membrane per millimeter of mercury of driving pressure.

Many factors other than the alveolocapillary membrane may affect the diffusing capacity. These include

1. Hemoglobin concentration
2. Elevated carboxyhemoglobin – e.g., in smokers
3. Pulmonary capillary blood volume – increased volume increases the D_{LCO}
4. Alveolar carbon dioxide concentration
5. Altitude
6. Technical variations

The most commonly used technique is the single breath – modified Krogh technique. Because there are many technical pitfalls and sources of variability in measuring D_{LCO} in conducting serial measurements in an aeromedical assessment, careful attention to technique in an accredited pulmonary function laboratory is especially important.

Diffusing capacity is generally decreased in interstitial lung diseases such as the pneumoconioses, or oxygen toxicity. D_{LCO} is also reduced in diseases causing loss of parenchyma such as emphysema. Many drugs may cause reductions in D_{LCO} because of their effects on the alveolocapillary membrane.

Recommendations for Pulmonary Function Assessment in Aeromedical Pharmacotherapeutic Evaluations

For drugs which have known or are suspected of having an effect on pulmonary function, pulmonary function testing should be included as part of the testing protocol. The precise PFT protocol may vary depending on whether the drug primarily has an effect on airway or interstitium. As a minimum, the following is recommended for baseline and serial evaluation.

- ◆ Assessment of airflow limitation – maximum forced expiratory curves
- ◆ Assessment of lung volumes – gas equilibration or body plethysmography
- ◆ Assessment of gas transfer – Single-breath diffusing capacity

Depending on the pharmacology and potential known adverse effects of the medication in question, the pulmonary function profile may be expanded to include:

- ◆ Assessment of airway reactivity and small airway function
 - low gas density spirometry
 - single-breath nitrogen washout
 - forced expiratory curve before and after bronchodilator
 - bronchial provocation testing
- ◆ Lung volume measurements with body plethysmography AND gas equilibration assessment for possible gas trapping

ENVIRONMENTAL ASSESSMENT

NATO air operations may require aircrew to deploy and operate in a wide range of environmental conditions, and may involve physiologic challenges including acceleration (G forces), altitude exposure including decompression and hypoxia, and extremes of thermal exposure. Life support equipment including PPG and CBW ensembles, flotation devices and cold water survival garments complicate physiologic responses. Medications for aircrew intended to enhance performance or for prevention or treatment of medical conditions may require assessment in such situations, where complex physiologic responses may occur in response to extreme environmental conditions. The

extent to which any individual medication must be assessed in terms of environmental responses will depend on the potential for altering responses in such environments, based on its chemical composition and mechanism of action.

RTO Working Group 26 recommends that an assessment of a medication being approved for unrestricted use in aircrew should consider the following:

- a. G-tolerance testing
- b. Thermal responses
- c. Hypoxic interactions

Thermal Responses

Air operations may impose high thermal strain on aircrew (such as were experienced in the Gulf War), or aircrew may face serious heat loss in cold ambient air or cold water immersion survival situations. Personal protective equipment such as PPG ensembles (Combat Edge, STING, AEA) or immersion suits may add to performance capability and/or survival on the one hand, but may compromise heat tolerance, and aircrew taking medications may be further compromised physiologically in such environments.

There are no established, standardized tests to assess heat or cold tolerance. Assessment of the potential impact of medications in hot or cold environments requires comparison with a placebo under clearly defined conditions. Test conditions should simulate to the extent possible those projected to occur operationally. The variables to be defined include:

- a. temperature
- b. humidity
- c. wind chill
- d. clothing and protective equipment worn
- e. physical activity – sedentary, workload – intermittent or continuous
- f. monitoring (depending on conditions)
 - core temperature; rectal probe, esophageal probe or radiotelemetry pill
 - skin temperature – number of sites
 - ambient temperature/dew point/humidity
 - heart rate
 - body heat gain

- sweat production
- evaporative efficiency

The Air Standardization Coordinating Committee has defined certain “Standard Environments” for the physiologic evaluation of personal thermal conditioning systems (ASCC AIR STD 61/62 Feb 88). These may be useful as guidelines to help define environments in which to assess the effect of medications. The guiding principle for assessing the thermal impact of medications in aircrew should be to simulate as closely as possible the most probable extremes of operational conditions.

Altitude

Altitude exposes aircrew to a potential threat from both hypoxia and decompression. Sudden loss of cabin pressurization or oxygen supply at high altitude represents an uncommon in-flight emergency which requires urgent aircrew action. Since this is an uncommon occurrence, with obvious action required, assessment of the incremental risk for decompression sickness or severe hypoxia is not considered essential in an aeromedical drug protocol, but may be included should the pharmacology or mechanism of action of the drug in question suggest a potential significant interaction in such circumstances.

Mild hypoxia, however, occurs routinely during normal air operations and the effect may be confounded by medications to create a significant flight safety and/or operational concern. Assessment of the environmental aeromedical effects of medications should include assessment of the potential interactive effects of mild hypoxia on cognitive function and performance.

Study design should be based on a double-blind crossover protocol to assess the interactive effects of mild hypoxia and medication on both performance and ability to learn new tasks (corresponding to the ability to respond to novel situations). Experimental design should ideally include an exercise component to simulate the physical workload of pilots (25W). Physiologic monitoring should include as a minimum heart rate and oxygen saturation. Performance tasks should include as a minimum a spatial orientation task (SOT, Manniken task), a serial choice reaction time (SCRT – e.g. Hamilton K et al), and a logical reasoning task (LRT- e.g., Baddeley). Study design should include a group trained to asymptote on

tasks before the hypoxia/drug intervention, and a second naive group who are first exposed to the tasks during the interventions (in a cross-over fashion) to assess the impact on novel task learning. Studies should ideally be performed at several altitudes ranging from 5,000-12,000 feet, but to minimize the probability of a type 2 error if a single altitude is chosen, 12,000 feet (3658 m) is recommended.

To assess performance differentially across subjects trained to asymptote versus those novel to the tasks, i.e., for subjects trained to asymptote, a learning curve demonstrating asymptote for the subjects is the normal pre-requisite to experimental manipulation. Subsequent to this demonstrated asymptote, the subjects are exposed to the experimental condition and perform multiple trials under the influence of the stressor in question. The performance results under the stressor are compared to the last trial or last few trials of the asymptote to determine the impact of the stressor.

Subjects who are novel to the task should perform multiple trials (without any previous exposure to the task) under the influence of the stressor, and these results are plotted over trials to produce a performance curve which is compared to the average learning curve (done by the other subjects i.e., the previously trained subjects), the difference in the curves showing the direct impact of the stressor on learning efficiency.

Acceleration

Centrifugal accelerative forces are a frequent physiologic challenge to fast-jet pilots, occurring to some degree on virtually all sorties. Protective systems have evolved since introduction of the g-suit over 50 years ago, with a see-saw balance between aircraft performance and human capability. Current generation aircraft with rapid onset high-G capability can produce G-LOC without warning and a series of accidents occurred until offset by G-training programs and improved G-protection. In the last few years the “push-pull” effect or negative to positive G-transition has been more clearly defined as a physiologic threat. New generation G-valves are being developed to provide protection based on G-history rather than just absolute G-levels. Future generation aircraft now in development will produce new challenges. In this challenging, changing scenario, every effort must be made with the introduction of a medication not to tip the balance against the human in the system.

Assessment of the impact on G-tolerance must be part of the investigation for any medication considered for use in fighter aircrew.

G-tolerance is best assessed on the human centrifuge. Various biometric assays for assessing G-tolerance have been published, but may not reflect the performance characteristics and physiologic demands of newer generation aircraft. There is significant intra-subject variability (Ludwig, Krock), and various end-points can be used including vision change (peripheral light-loss or central vision dimming), blood pressure or ear opacity. G-tolerance may be measured as +Gz intensity tolerance, or +Gz duration tolerance. Gz intensity tolerance may be measured in a relaxed state without straining, or with various +Gz protection including the AGSM (anti-G straining maneuver) and/or protective equipment from a standard G-suit to a full PPG protective ensemble.

WG 26 does not propose to define a precise methodology of assessing the effects of a medication in the acceleration environment, but rather to define a general approach. Such studies will by their nature be carried out in one of a few institutes or laboratories with human centrifuge capabilities, and researchers in such laboratories generally have extensive experience in biometric acceleration assays. The following concepts are outlined as general guidelines.

As a general guideline, a study to assess the effects of a pharmacologic agent on G-tolerance should be based on a double-blind cross-over design using subjects as their own control. Pharmacologic agents to be assayed, which will be prescribed in other than a single-dose regimen (e.g., pyridostigmine) should be given over a period long enough to reach a pharmacologic and physiologic steady state.

The following parameters constitute minimum recommended monitoring during a pharmacologic study assessment:

- electrocardiogram
- blood pressure (e.g., Finapres, with the cuff level standardized for all exposures at the third intercostal space)
- ear opacity monitor
- EMG activity from vastus lateralis, rectus abdominis and intercostal muscles to confirm that subjects are relaxed

Assessment of G-endpoint can be based on one or a combination of:

- peripheral visual loss
- central visual loss
- ear opacity

The following guidelines are recommended for assaying G-tolerance:

- Subjects should receive sufficient exposure and experience to be comfortable centrifuge riders.
- Baseline G-tolerance should be defined on at least three different days
- The intervention study (placebo, pharmacologic agent) should follow shortly after (within one week)
- G-tolerance profiles should include
 - relaxed gradual onset run with an onset rate of 0.1 G/sec
 - relaxed rapid onset runs with G-onset rates of at least 2 g/sec to plateaus with a maximum separation of 0.5 g

In addition to obtaining information on possible effects on G-tolerance in controlled studies, it is recommended that aircrew to whom long-term medications are prescribed undertake a standard G-training program once stabilized on the medication before returning to operational flying duties. This would allow individual aircrew to assess in a controlled environment any idiosyncratic drug effect on individual G-tolerance before returning to the operational environment.

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TABLE 1

DRUG	CHROMA-TOPSIA	DEFICIT TYPE	TINGE OR HALO	NOTES
Analgesics				
Acetaminophen			yellow	
Salicylates	+	I	yellow	
Antibiotics				
Chloramphenicol		II	yellow	Total dose > 100g or > 6 weeks
Chlortetracycline		III		The only tetracycline that affects color vision
Erythromycin		III	red, green	
Ethambutol		II, III		For 3-6 months, defect persists
Ethionamide				Heightened color perception
Isoniazide		II		
Penicillamine		II		
Streptomycin	+	II	yellow	
Sulfonamides	+	II	red, yellow	Transient myopia
Salazosulfapyridine		I		
Antifungal				
Griseofulvin			green	
Antipyretics				
Ibuprofen		II		Colors appear faded
Phenylbutazone		II		
Salicylates	+	I	yellow	
Antimalarials				
Atabrine	+			
Chloroquine	+	III +	yellow	Purple spots / white background
Clioquinole		II+, III		
Quinidine		II		
Quinine	+	I, II, III		
Antineoplastics				
Mercaptopurine		II		
Vincristine		II		
Antirheumatics				
Ibuprofen		II		Colors appear faded
Indomethacin		III		
Antispasmodics				
Atropine			red	Ocular administration
Cardiac and Vascular				
Amiodarone			halo	Glare from lights
Ergotamine	+	II	red	
Nitroglycerin			halo blue, yellow	
Rauwolfia alkaloids			yellow	Mainly reserpine
Digoxin		III	halo blue, red, yellow, green	Blue-yellow is early toxicity indicator
Digitalis	+	I+, II, III		
CNS effects				
Alcohol (ethanol)	+	II	halo blue	
Alcohol (amyl)	+	II		
Amphetamines			blue	

DRUG	CHROMA-TOPSIA	DEFICIT TYPE	TINGE OR HALO	NOTES
Barbiturates	+			
Isocarboxazid				
Methaqualone		I, II, III	yellow	
Oxazolinediones				Prolonged dazzle in light, objects seem snow covered
Pentobarbital			green, yellow	
Pentylentetrazol			yellow	
Phenothiazines			halo blue yellow	Rare in low doses
Diuretics				
Thiazides			yellow	Yellow spots in white field
Chlorothiazide	+	II		
Gases				
Carbon dioxide			yellow	
Ganglionic blockers				
Hexamethonium		III		
Heavy Metals				
Arsenicals	+	II		
Cyanide		II		
Lead		II		
Thallium		II		
Hormones				
Oral contraceptives		II	halo, blue	
Nitrofurane deriv.				
Furaltodone		I, II ?		
Nalidixic Acid	+			
MAO inhibitors		II		
Metal antagonists				
Disulfiram		II	red green	
Phenothiazine deriv.				
Thioridazine	+	I		
Tuberculostatics				
Dihydrostreptomycin		II		
Ethambutol		II, III		For 3-6 months , defect persists
Isoniazide		II		
PAS		II		
Rifampin	+	II		
Streptomycin	+	II	yellow	
Miscellaneous				
Strychnine	+			
Cannabis indica	+			
Tobacco (amblyopia)		II, III +		
Sildenafil citrate	+	II, III	blue, blue-green, yellow, pink	flashing lights, photophobia

Acquired color vision deficits have been categorized by means of a system devised by Verriest (1963). They are shown in the column labeled Deficit Type. Although not designed for that purpose, the system is often used to characterize color vision errors due to drug effects. The system is repeated here for convenience in viewing the table that follows.

TYPE I – a red-green deficit characteristic of retinal pathology in the posterior pole macula, where there are only “red” and “green” cones. There is an accompanying loss of visual acuity. The disease may progress to total color blindness and a nearly complete loss of visual acuity.

TYPE II – a red-green deficit with an accompanying milder loss of blue-yellow sensation. This problem is seen when there is optic nerve involvement as is seen in optic neuritis, retrobulbar neuritis, optic atrophy, optic nerve intoxication, or in tumors of the optic nerve or chiasm.

TYPE III – a blue-yellow deficit which is, by far, the most common acquired color vision defect. It occurs in choroidal, pigment epithelial, retinal and neural disorders including nuclear cataract, chorioretinal inflammations and degenerations, vascular disorders, glaucoma and many others.

Chromatopsia is a visual defect in which colorless objects appear to be tinged with color.

TABLE 2: Possible Adverse Pulmonary Reactions

Drug	Possible Pulmonary Reaction
Amiodarone	Acute pneumonitis, fibrosis,
ASA	Bronchospasm, NSAID sensitivity
ACE inhibitors	Cough
Beta-blockers	Bronchospasm
Betamethasone (inhaled)	Cough
Bromocriptine	Pleuritis, fibrosis
Carbamazepine	Hypersensitivity pneumonitis
Cromolyn (inhaled)	Cough
Dantrolene	Pleuritis, pneumonitis
Hydrochlorothiazide	Edema
Isoniazid	Pulmonary infiltrates
Nitrofurantoin	Hypersensitivity pneumonitis, fibrosis, pleurisy and effusion
NSAIDs	Bronchospasm, hypersensitivity pneumonitis, edema, fibrosis
p-aminosalicylic acid	Pulmonary infiltrates
Penicillin	Pulmonary infiltrates
Penicillamine	Bronchiolitis obliterans, hypersensitivity pneumonitis, fibrosis
Phenytoin	Hypersensitivity pneumonitis
Pilocarpine	Bronchospasm
Propafenone	Bronchospasm
Psyllium (inhaled)	Bronchospasm
Pyrimethamine compounds e.g., Daraclor, Maloprim, Fansidar	Hypersensitivity pneumonitis
Salicylates	Bronchospasm
Sulfasalazine	Hypersensitivity pneumonitis, bronchiolitis obliterans, fibrosis
Sulfonamides	Pulmonary infiltrates
Terbutaline	Edema
Tryptophan	Pneumonitis

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