THE EFFECT OF DRUG MITIGATED MOTION SICKNESS ON PHYSIOLOGICAL AND PSYCHOPHYSICAL PERFORMANCE

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The effect of drug mitigated motion sickness on physiological and psychophysical performance

by

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ABSTRACT

The purpose of this study was to measure physiological and psychophysical responses and cognitive performance of motion sickness (MS) susceptible individuals during exposure to a ship motion simulator. Further, this study investigated the effects of selected classes of anti-MS drugs in suppressing motion sickness induced effects upon physiological adaptations, psychophysical responses and cognitive performance. Thirteen healthy male and female volunteers were recruited to take part in this research (25.1 ± 2.3 years, 79.2 ± 14.6 kg, 174.4 ± 12.1 cm). Each participant ingested seven pharmaceutical preparations, 1 placebo and 6 anti-MS medications including Meclizine, Promethazine and Dexamphetamine, Promethazine and Caffeine, Dimenhydrinate, Scopolamine and Dexamphetamine and Chlorpheniramine prior to exposure to simulated ship motion on a 6 degree of freedom motion base. Sessions lasted up to one hour or until subjective MS ratings forced a termination of the trial. Subjective evaluations of MS symptom onset were taken using Graybiel's Diagnostic Criteria for Grading the Severity of Acute Motion Sickness and a 7-Point nausea rating scale. Defence Research Development Canada's Sustained Operations task batteries were employed to measure cognitive performance and were administered every 10 minutes throughout the motion exposure. Physiological measures, including core body temperature and skin temperatures were sampled continuously throughout the trial at 1 second intervals. A repeated measures ANOVA revealed no statistically significant differences in the physiological responses, however there was a significant difference found in the 7-point nausea scale rating evaluation of psychophysical responses. The placebo trial was significantly greater than any of the intervention trials. In addition to this significant difference, there were apparent rank order tendencies in response to the placebo and drug interventions. From these data there are trends indicating some drugs are better used in some scenarios, such as those requiring cognitive awareness and performance, while other drugs may be applied in situations where the main purpose is for the comfort of the passenger, or of someone whom vigilance and alertness is not required.

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Abbreviations:
MUN- Memorial University of Newfoundland
MS- Motion Sickness
MISC- Misery Scale
MSSQ- Motion Sickness Susceptibility Questionnaire
SMS- Full Mission Ship Bridge Simulator
HR- Heart Rate
GSR- Galvanized Skin Response
CMS - Centre for Marine Simulation
MI- Marine Institute of MUN
MEC- Meclizine
PROM + DEX- Promethazine + Dexamphetamine
PROM + CAF- Promethazine + Caffeine
DIM- Dimenhydrinate
SCOP + DEX- Scopolamine + Dexamphetamine
CHL- Chlorpheniramine

1.0 INTRODUCTION

Human performance has been shown to suffer decrements at the onset of motion sickness (MS) (Comperatore and Rivera, 1998). Thus it is important to prevent or mediate symptoms of MS in order to maximize performance efficiency and operator well-being. During a major NATO exercise in 1997, approximately one-half of 1025 naval subjects reported mild and moderate MS symptoms for sustained periods of time during operations in high seas (Colwell, 2000a). Those subjects in the group with mild and moderate MS symptoms reported substantially higher severity of problems with cognitive and physical performance, and with task completion than those with no MS symptoms. The types of problems reported and the potential consequences in terms of reduced operational effectiveness were sufficiently serious that it was suggested that these outcomes should be investigated further (Colwell, 2000b).

Motion sickness can present as a mild discomfort but can be severe and debilitating (McIntosh, 1998). It can cause a decrease in motivation that in turn results in a lower work rate and therefore a disruption or abandonment of the task (Wertheim, 1998). The common symptoms include malaise, yawning, abdominal discomfort, pallor (McIntosh, 1998; Takeda & Morita, 2001), drowsiness, headache, stomach awareness, endocrine changes (Haward, 2000), sweating, nausea, vomiting (Haward, 2000; McIntosh, 1998; Takeda & Morita, 2001) and cardiovascular changes such as tachycardia (Haward, 2000; McIntosh, 1998). Postural hypotension can also be present during motion sickness with the change in blood volume due to blood pooling in the lower extremities (McIntosh, 1998). It has been reported that blood flow changes and inactivity associated with seasickness exacerbate the development of hypothermia (Nobel et al., 2003). The underlying mechanisms responsible for core body cooling during bouts of MS are unknown and potential countermeasures for this additive effect on performance and survival require further investigation.

Intervention strategies, such as gazing upon an earth fixed reference, are often sought to mediate symptoms of MS (Bos et al., 2005). Most common are the use of pharmaceutical interventions to control MS symptoms. There are several classes of pharmaceutical medications on the market that can be consumed to aid in preventing the onset of motion sickness (eg. antihistamines, anticholinergics (antimuscarinic/antihistamines) and sympathomimetics). Medications are most effective when taken prior to exposure to the motion environment. Once vomiting occurs, it is near impossible for the oral medication to stay in the body long enough to penetrate the blood stream.

Using medications such as scopolamine and Dramamine to mediate symptoms of motion sickness will often result in drowsiness and fatigue. Consequently stimulants are added to the medications in order to counteract the effect of drowsiness in the medications.

While it is clear that optimal performance in command and control situations is critical, other related maritime demands may also be considered. Liferaft and lifeboat occupants can be exposed to a considerable amount of motion during evacuation and recovery situations. Experimental evidence indicates that a high percentage of liferaft occupants will experience severe symptoms of MS (MacKinnon et al., 2005). Training regimes should plan primary prevention strategies to manage liferaft passengers who might get MS during abandonment. Search and Rescue Technicians are also exposed to the same provocative conditions as those they are trying to rescue. Prevention of motion sickness while maintaining the ability to perform arduous physical tasks and maintain cognitive awareness and vigilance is of paramount importance to many.

Leisure travelers and recreationalists who are exposed to provocative ship motions, car motions and air travel also face the potential performance decrements, and general malaise as a result of motion sickness. Arriving in an unfamiliar place and having to drive a vehicle while suffering from residual motions sickness symptoms after debarking a ferry or airplane can result in disastrous outcomes.

1.1 Objectives of Work

The objectives of this work are to:

1. measure physiological adaptations, psychophysical responses and cognitive performance of motion sickness susceptible individuals during exposure to a ship motion simulator.
2. investigate the effects of selected classes of anti-motion sickness drugs in suppressing motion sickness induced effects upon physiological adaptations, psychophysical responses and cognitive performance

1.2 Hypotheses

The following null hypotheses were tested:

H1: Core body temperature will remain unchanged due to the onset of motion sickness or the introduction of anti-motion sickness medications

H2: Skin temperature will remain unchanged due to the onset of motion sickness or the introduction of anti-motion sickness medications

H3: Galvanic skin responses will remain unchanged due to the onset of motion sickness or the introduction of anti-motion sickness medications

H4: Cognitive performance will remain unchanged due to the onset of motion sickness or the introduction of anti-motion sickness medications

1.3 Assumptions and Limitations

The following assumptions were made:

1. Although these research findings are intended to provide guidance to seagoing personnel, for the purposes of this research volunteer subjects were sampled from the general public, which included people from a range of employment status, socio-economic status and age that may not necessary reflect the demographics of working mariners.
2. It remains difficult to recruit subjects who are susceptible to motion sickness. Those who are susceptible quite often refuse to volunteer for such studies. Furthermore, the protocol included seven repeated measurement sessions. A rectal probe was used to measure core body temperature. Many found this an invasive and perhaps embarrassing measurement to undergo, and may deter some from volunteering to participate, as was the case during recruitment in this study. Subjects were given detailed instructions regarding probe self-insertion and were enclosed in a comfortable and private room in order to perform this task. Recruitment strategies included a description of the research study and assurances that symptoms such as vomiting and retching would be avoided and was not the purpose of the study. With ethical approval by the University's Human Investigations Committee, subjects were offered an honorarium for participating in the study.
3. The motion conditions simulated in the experimental protocol were based on mathematical models of ship and water interactions. Scaling factors were used to accommodate the physical capacity of the ship motion simulator.
4. One of the metrics required a self-report of MS symptoms being experienced by the subject. Familiarity with this scale would influence the quality of the reported score. Care was taken in explaining the MISC Scale.

2.0 REVIEW OF LITERATURE

2.1 Prominent Contemporary Theories of Motion Sickness

Since motion sickness was first identified, scientists and sufferers alike have been trying to understand causes and create theories to explain what it is and why it afflicts living beings. Early documentation attributed motion sickness to gastric upset, circulatory disturbance and various internal incongruencies (Reason and Brand, 1975). Early work supported the vestibular/proprioceptor theories that referred to vision, nervous system function, and muscle activity as the main sensory stimuli alerting the body to environmental changes and that influenced motion sickness.

Reason and Brand (1975) developed a theory to explain their understanding of motion sickness based on a culmination of current views on motion sickness, the work they were doing, and expansion on what was happening in the field of research. This theory stimulated new approaches towards motion sickness research. Their sensory rearrangement theory consists of two main types of sensory rearrangement. The first is visual-vestibular; which indicates one type of motion from the eyes and another from the vestibular system (located in the inner ear), which is responsible for internal sense of balance. The second is canal-otolith; where the canals of the inner ear respond to rotation and the otoliths of the inner ear signal lateral translation. These are then further divided into two types of conflict. Type one conflict is when the two sensory systems relay opposing motion information, as in horizontal and vertical input, and type two is when one system signals motion, e.g. vertical, and the other system signals no motion (Reason and Brand, 1975). Another type of vestibular-proprioceptor rearrangement was added to the model as a third type of sensory rearrangement, which indicates a conflict between physical sensations of motion and internal information of motion (Guedry, 1991).

Oman (1982) enhanced Reason and Brand's theory of sensory rearrangement by defining it with a mathematical formula. In his model, vectors are used to represent the change in

sensory information. This vector difference between perceived and actual movement grows as people become more susceptible to motion sickness, and symptoms grow more severe.

The ecological theory of motion sickness and postural instability (Ricco and Staffrogen, 1991), was developed after an extensive review of sensory conflict and sensory rearrangement theories. They discovered that "...virtually all work in the area of motion sickness is motivated by a common set of fundamental assumptions. These assumptions find their most explicit expression in the sensory conflict view..." (Ricco and Staffrogen, 1991, p160). The sensory conflict theory, as they see it, indicates that there is something wrong with sensory stimulation; however they see sensory stimulation as equal in both provocative and non-provocative situations. They hypothesize that animals become sick in situations in which they do not have, or have not yet learned, strategies to maintain postural stability. They refer to the vestibular system's role in processing the environmental information to maintain stability and thus this theory, although with a fundamentally different paradigm to approach the study of motion sickness, has some crossover nonetheless, with the conflict theory.

Bles et al. (1998) carefully reviewed Reason and Brand's sensory rearrangement theory and subsidiary theories (Guedry, 1991; Oman, 1982) to come up with a theory they believe incorporates all forms of sensory rearrangement into one type of conflict: "All situations which provoke motion sickness are characterized by a condition in which the sensed vertical, as determined on the basis of integrated information from the eyes, the vestibular system and the nonvestibular proprioceptors, is at variance with the subjective vertical as predicted on the basis of previous experience" (Bles et al., 1998, p482). Bles and Bos (2006) later changed the term "subjective vertical" to "expected vertical" to better fit their theory.

The sensory rearrangement theory (Reason and Brand, 1975), and expanded upon by Oman (1982), Guedry (1991), Bles et al. (1998) is widely researched and supported and is the foundation of much of the research currently being done. The ecological theory of motion sickness and postural instability presented by Ricco and Staffrogen (1991) is relatively new and so has not been as extensively used in clinical experiments. These theoretical foundations allow researchers to further develop experimental conditions under which they may continue to explore the underlying causes of motion sickness.

2.2 Types of Motion Sickness

There are several types of motion sickness. Sea, car, air, space and simulator sickness are all common manifestations of the ailment that most persons are familiar. Although each form of motion sickness is similar, and can be sufficiently described using the sensory conflict theory, the provocative motion stimulus involved in each is unique. Motion sickness manifests in a number of symptoms regardless of the motion exposure causing the sickness. The commonly reported symptoms of motion sickness as described by Graybiel et al. (1968) are (in increasing severity) nausea, sweating, pallor, gastric discomfort and vomiting.

Seasickness is likely the first form of motion sickness that was experienced by man (Griffin, 1991; Reason and Brand, 1975). The movement of a ship at sea can be an extremely provocative stimulus. The motions of waves can be unpredictable and severe for a long time, and the stimulus cannot be removed easily without returning to land (Reason and Brand, 1975). The contributions of roll, pitch and heave to seasickness were evaluated (Wertheim, Bos, and Bles, 1998). It was discovered that roll independently and roll and pitch combined both had slight motion sickness inducing effects, but were not as significant as the combination of all three. They found that even the addition of a small amount of heave significantly increases the provocative value of pitch and roll motion. This type of tri-axial stimulation, roll, pitch and heave, is unique in its

variability, and unlike other types of movement in common forms of terrestrial transportation.

Carsickness in passengers is often related to travel experience (Gahlinger, 2000; Turner and Griffin, 1999). Youth tend to be more susceptible and incidence declines with age and travel experience (Reason and Brand, 1975). Other predominant factors in determining carsickness are the size of the visual field and the variability of car motions. A study evaluated visual field effects and motion sickness in cars (Griffin and Newman, 2004). Ultimately, the findings showed that even a narrow view of the road ahead reduced sickness more so than even a real time video projection of the road ahead, possibly because of the movement of the camera. Subjects who were blindfolded or had no external view produced similar levels of sickness. The seating position of the subject was not found to be a factor contributing to motion sickness.

Vogel, Kohlhaas, and Baumgarten (1982) examined the effect of linear acceleration in automobiles and motion sickness. They found that horizontal acceleration using multiple braking maneuvers is an effective motion sickness producing stimulus. Further, they found that acceleration in the backwards facing position was a more profound nauseogenic stimulus than the front facing position, including experiments that had subjects blindfolded.

A large number of crew will experience airsickness at some point in their careers. Most often this will occur during training (Stott, 1990). The conflict that is experienced in airsickness is the effect of changing gravity when the aircraft is in turbulent conditions. Head movements made in turbulent conditions with changing gravity are not well tolerated in susceptible individuals (Bles et al. 1998). Kennedy et al. (1972) examined three types of aircraft penetrating a hurricane and the motion sickness provoking effects of the weather. Of the experienced crewmembers only one eventually experienced emesis. Of the twenty-one experienced crew members and the research team there were only two who experienced no symptoms.

Space sickness distinctly differs from other forms of motion sickness, as it is the expression of motion sickness symptoms in zero/micro gravity. Symptoms differ from motion sickness in conditions of normal gravity. Astronauts typically experience no sweating; flushing more so than pallor, and vomiting is sudden, without nausea. Non-susceptibility occurs after three days when motion sickness symptoms disappear, maybe because of a lack of reference to down. Space sickness, like other forms of motion sickness, may well be attributed to the vestibular system receiving false information. Throughout weightless flight, external reference points do not correspond with sensory input causing a sensory conflict. There is some inconsistency as to what symptoms are typical in space sickness (Money, 1991). Little information is available regarding the severity of space sickness, likely due to of the lack of reported motion sick symptoms. The importance of the job and the requirement to be functioning at optimal levels is presumed to deter sufferers from accurately reporting illness (Money, 1991). Space sickness can have debilitating effects that are likely to reduce efficiency in an environment that does not tolerate error (Reason and Brand, 1975).

Simulators are commonly used to reduce the cost and risk of training pilots and drivers (Money, 1991; Mourant and Thattacheny, 2000). Specific limitations of simulators are the ability to replicate actual movements, and the ability to reproduce an accurate visual scene. Visual simulators are known to produce symptoms of motion sickness because of poor representation of self-motion. That is, the eyes give the sense that the body is moving with the references given by the simulator, however, the body senses that it remains stationary (Kennedy et al., 1990). Also, simulator users are finding that as technology improves the problem of motion sickness gets worse. Simulator sickness incidence varies and paradoxically, is most common among newer pilots with little experience on a simulator and pilots with more real life experience (Money, 1991).

2.3 Incidence and Predictors of Motion Sickness

Within any situation it proves helpful to be able to predict an individual's susceptibility to motion sickness stimuli. In experimental settings, screening subjects for motion sickness susceptibility with stringent criteria is crucial to describing the research sample. It is also crucial to some professional training programs to know in advance if it is worthwhile to expend the resources to train a fighter pilot, or an astronaut, before knowing whether the candidate can work reliably in motion-rich environments.

There are a number of ways to assess an individual's susceptibility to nauseogenic stimuli. The range in feasibility and cost effectiveness of these assessments has resulted in fine-tuning personal history questionnaires, and developing mathematical formulas to predict motion sickness incidence in provocative motion situations.

Assessment techniques include both actual exposure to motion and questionnaires. Motion exposure techniques subject the individual to accelerative stimuli and then grade susceptibility. The swing test and coriolis techniques (vestibular adroitness test, dial test, and the brief vestibular disorientation test) are well known actual exposure tests (Reason and Brand, 1975; Golding, 2006).

Questionnaires take a tally of past motion experiences and their effect on the individual as rated by the severity of motion sickness symptoms. Reason and Brand (1975) developed a motion sickness susceptibility questionnaire (MSSQ) comprised of two sections, one to assess motion sickness events up to twelve years old, and one to assess the number of events in the last ten years. Administering questionnaires is timely and subjects are usually able to recall experiences easily, without the need to induce sickness. The most common problem with questionnaires is that groups who will be evaluated based on their scores (eg: pilots) may not always be truthful (Reason and Brand, 1975).

Golding (1998) reported that many subjects have not found the original Reason and Brand version of the MSSQ easy to complete without guidance and explanation. He developed a new MSSQ-Long to be more easily completed by subjects, and to simplify the scoring. The MSSQ-Long was tested over several pilot studies, and then later administered the test to a larger group of university students and to a group of patients undergoing chemotherapy. Ultimately, he found that the questionnaire was both easy to understand and complete by the subjects. As well the MSSQ-Long provided adult reference norms almost identical to those presented in the original MSSQ and the internal validity was high. Golding suggests that the revised MSSQ may be used as a direct replacement of the original (Golding 1998).

Golding (2006) later revisited the MSSQ-Long and Reason and Brand's MSSQ (1975) to create a shorter questionnaire that would ultimately retain validity and speed-up evaluations. At eighteen questions, it is one-third the length of the MSSQ-Long (Golding 2006). To condense the number of questions a repeated item analysis was conducted with various scoring methods. Technology based questions were removed as they showed little significance and vomiting-specific questions were removed. Both the MSSQ-Long and MSSQ-Short were administered to subjects exposed to provocative motion in a controlled laboratory setting. The predictive validity of the MSSQ-Short was comparable to the previous MSSQ-Long, with the only drawback being that the MSSQ-Long had a higher predictive value for highly susceptible subjects (Golding 2006).

Powell et al. (1962) tested a motion history questionnaire (MHQ) on all new recruits of the Royal Canadian Air Force (RCAF) in 1960-61. There were 151 recruits in the study and 14 of them failed (based on their scoring criteria) both the MHQ and the actual exposure airsickness test. They found the MHQ a significant measure approaching the $p<0.01$ level. They did not find the combination of MHQ and actual testing to be any better a predictor that the MHQ alone. It is interesting to note that, of these 14 who failed

the tests administered by Powell et al., five later failed out of RCAF training later due to motion sickness.

O'Hanlon and McCauly (1974) developed an empirical method for predicting motion sickness incidence (MSI) by exposing subjects to single-frequency, sinusoidal, vertical motions (Colwell,1989) The model predicts MSI (%) using magnitude, frequency and duration of vertical accelerations. Using this formula in a situation that emulates the original study they find this a reasonable measure of MSI.

2.4 Effects of Motion Sickness on Performance

Implications of motion sickness on performance are of critical importance when executing rescue operations, operating commercial transport vehicles, when crew are performing tasks during motion, and maintaining the operation of a moving vehicle. Motion sickness may negatively impact both the physical ability as well as the cognitive function of those in passenger, crew and command positions. There is often low or no tolerance of error when operating spacecraft, marine vessels, or in mass transport.

Evaluating the effects of the Command and Control environment on soldier health and performance observed a negative effect on the soldiers when they attended to computer screens while the vehicle was moving (Cowings et al., 1999). Short breaks did not alleviate the decreases in performance, and mood and performance were both impaired in the vehicle. Malaise and drowsiness were among the most frequently reported symptoms of motion sickness and had a negative impact on the soldier's operational efficiency. All 24 soldiers reported symptoms of motion sickness, 55% of them were moderate to severe symptoms, and 15% of subjects experienced vomiting.

The susceptibility to motion sickness was measured in crew operating three types of aircraft during hurricane penetration (Kennedy et al., 1972). Only two of 39 people involved in the study, including the subjects, the researchers, and the experienced

crewmembers did not experience any symptoms of motion sickness, and they were experienced crew. The range of symptoms reported varied from mild to motion sick with vomiting. Of the individuals involved in the study, four experienced emesis and one was an experienced crewmember. In this study, the more severe the conditions were, the poorer the scores on the tests of performance were. Performance generally continued to deteriorate except in one type of aircraft, where performance began to improve when the aircraft began its return to the base, and these results may be partly attributed to habituation.

Space motion sickness has been reported, however, it has been suggested that perhaps it is under-reported due to the intolerance of error and high expectation of performance during space missions (Reason and Brand, 1975). Kelly et al. (2005) evaluated crewmember performance before, during and after spaceflight. The only changes in performance were during spaceflight where response time during number recognition tasks and digit-symbol substitution increased.

In a report by the US Coast Guard, Comperatore and Rivera (1998) evaluated crew fatigue and performance on coast guard cutters. Decrements were seen in the day-to-day testing where the researchers expected to see improvements due to a learning effect. The sea motion affected the motivation of the crew, although perceived motion discomfort was rated fairly low. Due to a perceived lack of anonymity during recruitment and testing within the military environment, military personnel fear that accurate subjective reporting in a negative manner may impact their job status, especially if they are reporting discomfort in their primary working environment, such as a sailor reporting motion sickness at sea. Therefore it is difficult to validate subjective reports, as sometimes subjective and objective reports will be at odds. Fatigue was a factor that influenced performance, and the mean fatigue rating throughout the testing period remained at about the level that suggested the crew were losing interest in staying awake (about 42 on a scale of 1-100, 1 being wide awake).

The effect that motion has on performance may also be related to the extent the task distracts the individual. Bos et al. (2005) evaluated the visual effects on motion sickness in a ship motion simulator. The effects of inside, outside and no view were evaluated, using performance on cognitive tasks as a measurement tool. Their findings indicated no differences between the groups that could not be attributed to the conditions of the experiment (i.e. the no view group used auditory tasks as opposed to visual tasks as in the inside and outside (fixed horizon) groups), however, reported symptoms of motion sickness decreased when subjects were blindfolded. Blindfolding removes all visual cues of motion, for example movement of a curtain or a pencil rolling gives a visual cue to the brain, which may be different from the proprioceptive cues of motion being communicated to the brain. Relying only on proprioceptive cues of motion removes the mismatch that is observed otherwise contributing to the development of motion sickness. Reason and Brand (1975) also suggested that task performance might abate motion sickness symptoms.

There is a relationship between task performance and motion sickness symptoms. The magnitude of motion stimulus, the type of task and the level of comfort with both the task being performed and the surrounding environment all have a role in how severely or how detrimentally one may affect the other. In studies by Kennedy et al. (1972), Comperatore and Rivera (1998), and Cowings et al. (1999) perhaps the decrement in performance may be attributed to the onset of motion sickness prior to performance. Conversely in the study by Bos et al. (2005) the subjects are performing their tasks at the time motion sickness symptoms would be developing and in this case their cognitive preoccupation may impede these symptoms.

2.5 Prevention and Treatment of Motion Sickness

Preventing the onset of motion sickness symptoms is critical for both the operation of vehicles and enjoyment and ease of travel. There are dozens of medications to treat and

prevent motion sickness. Many of them are considered reliable and are repeatedly tested and measured alone, and in various combinations. While the underlying mechanisms of motion sickness are still in question, researchers experimenting with new drugs in the treatment of motion sickness are continually finding formulations which mediate or eliminate symptoms of motion sickness.

Scopolamine (hyoscine) and d-amphetamine in combination are most frequently and effectively used as treatment (Wood et al., 1990, Wood and Graybiel, 1970a Wood and Graybiel, 1970b, Wood et al. 1968). Promethazine is often the second drug of choice (Wood and Graybiel, 1970a; Wood et al., 1968; Wood and Graybiel, 1970b; Graybiel, 1970), and is frequently used by NASA to treat space sickness (Yates, Miller, and Lucot, 1998).

Used to treat seasickness in a study by Holling, McArdle, and Trottter (1944), scopolamine was found to be an effective dose at 0.6 mg, whereas at 1.2 mg the subjects complained of dry mouth, although they were not drowsy. However, in a study comparing seven commonly used anti-motion sickness drugs on the prevention of seasickness, Schmid et al. (1994) found that the subjects using scopolamine on its own have a tendency to more illness than the other treatment groups. A study of the effects of transdermal scopolamine at 12 and 72 hours after administration showed mixed results (Graybiel et al., 1982). The first application resulted in four beneficial responses after 12 hours and none after 72, where in the second application there were four beneficial responses after 12 hours and three after 72. One subject experienced severe side effects that did not diminish after the 72 hours. The variability in these results are attributed to the possibility of poor functioning of the transdermal patch system and temperature, indicating more effective absorption in warmer weather. Nachum et al. (2006) support the use of transdermal scopolamine use for long duration travel (6 hours or longer) especially when oral doses may not be effective, or tolerable.

Wood et al. (1965) evaluated nine anti-motion sickness drugs using the Slow Rotation Room. Their findings showed that scopolamine increased the subjects' average tolerance to the stimulation by 147% compared to placebo, and d-amphetamine increased tolerance by 70% as compared to placebo when used alone. When scopolamine and d-amphetamine were used in combination, Wood et al. observed an increase of 194% in tolerance to the stimulation.

Another study by Wood and Graybiel (1968) using the Pensacola Slow Rotation Room evaluated the effectiveness of 16 anti-motion sickness drugs. The drugs tested fell into four categories: sympatholytic, antihistamines, sympathomimetic and parasympatholytic. Their findings were very clear indicating that combinations of sympathomimetic (amphetamine) and parasympatholytic (scopolamine) drugs are significantly more effective in treating all symptoms of motion sickness including nearly eliminating side effects such as drowsiness and dry mouth at the 0.6mg scopolamine and 10 mg amphetamine dose.

Based on the findings by Wood and Graybiel (1968), a new understanding of the mechanisms involved in the development of motion sickness was proposed (Wood and Graybiel, 1970). They suggested that competing neural systems, one activated by acetylcholine and one by norepinepherine, might be involved in motion sickness. This idea was reiterated when evaluating the effects of anti-motion sickness medications on secondary symptoms of motion sickness (Wood et al., 1990). Long after nausea and vomiting have subsided secondary symptoms negatively affect performance, cause drowsiness and slow brain waves. Based on the results of the evaluation of anti-motion sickness medications on secondary symptoms, Wood et al. (1990) hold that the combination of scopolamine and amphetamine is the most effective in treating both nausea and vomiting, as well as treating the secondary symptoms of motion sickness.

Antihistamines such as promethazine 25 mg, diphenidol 50mg and dimenahydrate 50 mg (Dramamine) ranked next to sympathomimetic, and parasympatholytic drugs in effectiveness (Wood and Graybiel, 1968). Though not as effective as other drug classes, they have a longer protective duration and are safer (Yates et al., 1998; Wood and Graybiel, 1970). A study by Strickland and Hahn (1949) found that Dramamine prevented airsickness in 71.3% of 108 subjects, compared to 44.4% when administered a placebo. Schmid et al., (1994) studied the effects of seven commonly used drugs to prevent seasickness. Their findings showed that dimenahydrate 50mg combined with caffeine 50mg (Dramamine) was the most effective in preventing motion sickness symptoms, and cinnarizine 20mg combined with domperidone 15mg (Touristil) a close second.

Aside from the resounding support for several effective pharmacological treatments for symptoms of motion sickness, there are also alternatives being explored. A study of 24 healthy subjects exposed to Coriolis stimulation evaluated controlled breathing and listening to a music audiotape to control motion sickness symptoms (Sang et al., 2003). Compared to the no intervention group both controlled breathing and listening to music delayed the onset of mild nausea. Although these methods are only half as effective as drugs at increasing tolerance to provocative stimulus they note the benefits of these methods being free of side effects, inexpensive and easy to implement. Ginger has also been used for subsiding motion sickness related nausea, possibly by preventing gastric dysrhythmias (Lien et al., 2003; Ernst and Pittler, 2000). Schmid et al. (1994) found ginger (250mg) to be equally as effective in preventing motion sickness as cinnarizine (25mg).

There are several treatments shown to be effective to delay or treat motion sickness symptoms, both pharmacological and otherwise. The evidence shows that any of these measures will increase resistance to stimulation over using no treatment at all. For the lay traveler choosing an inexpensive, over the counter drug may be a quick fix for their

discomfort, but the solution is not so clear for those who are in command of the vehicle or vessel. Often, habituation occurs after repeated exposure to similar types of provocative motion (i.e.: new pilots or crew on a ship will become accustomed to the motions and they will no longer be motion sick inducing). In very few cases motion sickness never subsides, and in these individuals appropriate treatment must be found, or they may end their career. The severity of symptoms versus the side effects of drugs must be carefully weighed when they are treating symptoms of motion sickness for individuals in command or control positions.

2.6 Gaps in the Literature

Motion sickness has been explored in many ways using both actual and simulated motion experiences. How performance is maintained during the motion exposure has been researched under various operational or experimental conditions, little research has examined the effects of various mediating pharmaceuticals in a well controlled motion environment. Similarly, examining the effects of moderate motion sickness on physiological and psychophysical responses remains limited. This research contributes to this gap in the current literature.

3.0 METHODS

3.1 Subjects

Thirteen apparently healthy male (8) and female (5) volunteers (25.1 ± 2.3 years of age, 79.2 ± 14.6 kg, 174.4 ± 12.1 cm) were recruited to participate in this study. Participants were recruited by posters (Appendix A), various electronic media, and by word of mouth. This study was granted ethical approval from MUN HIC.

Participants were given a written copy of the protocol and a verbal explanation of the experiment, including the expectations of the subject, the roles of the investigator and the participant's right to voluntarily withdraw from the experiment at any time. Participants were fully informed of the purpose, details, discomforts and risks associated with the experimental protocol before being asked for their written informed consent. The risks and discomforts included self-insertion of a rectal thermometer, motion sickness symptoms elicited by the ship motion simulator, exposure to cold and side effects from the experimental interventions, such as drowsiness. Volunteers who agreed to participate were required to read, understand, discuss and agree with the subject consent form (Appendix B) and the invasive medical procedures consent form (Appendix C) per Memorial University of Newfoundland Human Investigations Committee (MUN HIC) guidelines, and to signify this agreement by signing these consent forms. In order to participate, all volunteers were required to be in good general health, with no known history of vestibular or occulomotor disease. Health status was screened using a Medical History Questionnaire (Appendix D). This study was granted ethical approval from MUN HIC.

Volunteers who were deemed healthy and able to participate were further screened for susceptibility to motion sickness. In the present study recruitment was a difficult task, asking for a large time commitment over an extended period, and the experimental conditions asked that subjects voluntarily subject themselves to undesirable conditions

(moderate cold environment, sickness potential, probes and sensors). Based on these factors, subjects with high susceptibility for motion sickness needed to be selected.
Each subject completed the Motion Sickness Susceptibility Questionnaire (Appendix E) to determine their susceptibility to motion sickness. The mean MSSQ score was 127 (±43.2, min 63.9, max 217.4). Golding and Kergueulen (1992) suggested that a score of 68.9 corresponded to a person that was more susceptible than would be expected from the normal population.

Participants were asked to maintain normal daily activities, consume a light meal prior to each trial and to refrain from alcohol and the use of cold and allergy medications (such as antihistamines, antimuscarinic and anticholinergic drugs) for 36 hours before each experimental session. Participants were asked to inform the researcher of any changes in health status since their initial assessment; including but not limited to viral illnesses, new prescription or "over-the-counter" drugs, and new risk of pregnancy within a week of the actual experiment.

3.2 Experimental Design

3.2.1 Anti-Nauseant Medications

A randomized double-blind repeated-measures protocol was used to assess the impact of the anti-nauseant medications upon both physiological responses and psychomotor performance. All participants participated in 7 trials with at least a 7-day washout period in between trials. Data collection occurred at the same time of day, on the same day of the week for each subject. The participants ingested one of 6 anti-motion sickness drugs and a placebo prior to exposure to the simulated motions. The researcher verified that participants ingested the designated medication two hours prior to arriving at the Centre for Marine Simulation (CMS) for the data collection session.

The anti-motion sickness drugs and their characteristics are listed in Table 3.1 and are available for personal use through a physician's prescription. The test doses are standard clinical amounts. All formulations prescriptions were provided by the Defence and Research Development Canada – Toronto. In order to maintain the double blind protocol of this study, all medications were prepared in identical capsule format by a contracted pharmacy (Central Medical Pharmacy, Toronto, ON, Canada). This company maintained the coded drug information until release to the experimenters following the completion of the data collection portion of the study.

3.2.2 Motion Simulator

The study was performed in the Ship Motion Simulator (SMS) of the Centre for Marine Simulation (CMS), at the Marine Institute of MUN. This facility is a large ship bridge (5m x 7m), mounted upon a six degrees of freedom motion base, and surrounded by 360° azimuth coverage by visual projection screens (Figure 3.1).

Figure 3.1: Ship Motion Simulator

Table 3.1: Name and description of drugs employed in study.

Drugs and dosage	**Optimal effect time**	**Known side effects**	**Known drug interactions**
Meclizine (Bonamine®) 50 mg,Antiemetic (MEC)	Acting 2 hours after ingestion, effects lasting 8-12 hours	Drowsiness, dry mouth, fatigue	Increased CNS depression with other CNS depressants
Promethazine 25 Mg + dexamphetamine 10 mg, Antihistamine (PROM+DEX)	Acting 2 hours after ingestion, effects lasting 8-12 hours	Drowsiness	Increased drowsiness with antihistamines
Promethazine 25 mg + caffeine 200 mg, Antihistamine (PROM+CAF)	Acting 2 hours after ingestion, effects lasting 8-12 hours	Drowsiness	Increased drowsiness with antihistamines
Dimenhydrinate (Gravol®) 50 mg, Antihistamine (DIM)	Acting 2 hours after ingestion, effects lasting 8-12 hours	Drowsiness, dry mouth	Increased drowsiness with antihistamines
Scopolamine 0.8 mg + dexamphetamine 5 mg, anticholinergic (SCOP+DEX)	Acting within 30-60 min after ingestion, effects lasting for about 4 hours	Drowsiness, dry mouth	
Chlorpheniramine (12 mg), Antihistamine (CHL)	About 3 hours after ingestion, effects lasting for about 5 hours	Drowsiness and dry mouth	Increased drowsiness with antihistamines

The SMS produces motions for a real-time ship simulation. The key variables are the size and shape of the hull, the ship speed and course, the wave height, wave period (or wave length) and wave direction. The motions for the experiment were developed for a relative wave direction of approximately 45° off the bow, and with a frequency of vertical motion of approximately 0.2 Hz. The ship motion simulator being used for the experiment has both software and hardware safety interlocks to prevent loss of control and to avoid excessive motions. This facility is ISO 9001 certified, and it has a safe operating history of over ten years use as a motion platform for research projects and maritime certification programs delivered by the Marine Institute of MUN.

The subject placement was standardized within the simulator cabin (see Figure 3.2). A chair and desk were placed on the left wing of the bridge. Non-slip pads were placed beneath the desk legs and chair legs to prevent sliding during the motion. Researchers at MUN have used this set-up previously, and motions provide no threat for extreme subject instability (Colwell and MacKinnon, 2007, Bos et al., 2005).

The internal cabin temperature of the simulator was maintained at 10 ± 0.5°C. A temperature sensor was employed to ensure a stable internal cabin temperature was maintained throughout the data collection period and across each trial.

Figure 3.2: Subject placement in the SMS

3.2.3 Physiological Measurements

Upon arrival at the Center for Marine Simulation (CMS) the participant was prepared for each data collection trial. Rectal temperature was measured using a Philips 400 series thermistor (model 21090A, Philips Medical Systems) subject-inserted 15cm into the rectum. Each subject had been previously briefed on how to self-perform this procedure (see Appendix F) and to have the subject assure that the insertion was done to a specified depth. The subject then dressed in shorts, shirt, socks and comfortable shoes and presented themselves to the investigator. The investigator applied the skin temperature sensors (SA1-RTD surface temperature sensor, Omega Engineering, Inc. Stamford, CT.) to seven sites (Hardy and Dubois, 1938): forehead, deltoid, hand, abdomen, upper anterior thigh, shin, and foot. Refer to Table 3.2 for description of anatomical landmarks used to position sensors.

Table 3.2: Table of anatomical landmarks for placement of skin temperature sensors.

Location	**Anatomical Landmarks**	**Weighted values (Hardy and Dubois, 1938)**
Forehead	Half-way between eyebrows and hairline, centered between the eyes	0.07
Deltoid	In the centre of the deltoid on the lateral aspect of the arm.	0.14
Hand	Posterior, 2.5 cm from the wrist, centered over the metacarpals.	0.05
Abdomen	5cm to the left of the omphalion	0.35f
Upper anterior thigh	Midway between the inguinal fold and the superior border of the patella	0.19
Shin	Midway between the talocrural joint and the superior point of the tibia	0.13
Foot	On the dorsal surface, centered over the metatarsals	0.07

The investigator then secured the galvanic skin response (GSR) electrodes (S220 Galvanic Skin Response Sensor, Qubit Systems, Kingston, ON) to the index and middle fingers of the non-dominant hand and measured change in sweat gland activity, a response of the sympathetic nervous system (see Figure 3.3).

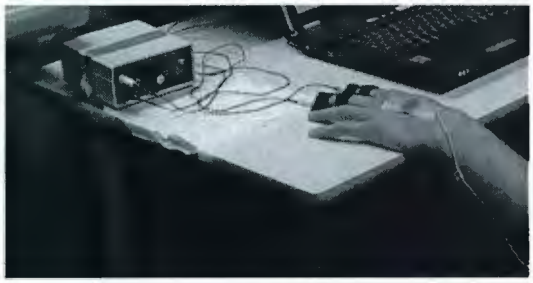

Figure 3.3: Galvanic Skin Response setup

The time-histories for each physiological variable were collected throughout the data collection period. The analogue signal for each physiological measure was sampled at 2 Hz then converted via an analogue to digital converters and stored on a computer for later analyses.

3.2.4 Psychomotor Measurements

Prior to commencement of the study, all subjects underwent an habituation period to familiarize themselves with the nature of the psychomotor tests (DRDC Toronto Sustained Operations (SUSOPS) package). This was to ensure that a learning effect was not being measured in the subsequent experimental trials. The investigator confirmed with each participant that s/he understood the demands of the SUSOPS tasks.

The battery of SUSOPS tests completed as a baseline measure and during specific intervals during the motion exposure took three minutes to complete. During motion

exposure the tests were performed at ten-minute intervals starting at minute seven. The computer-based Cognitive Test Battery combines three tests from the DRDC Toronto Sustained Operations (SUSOPS) package. The test battery employed in this study included 1 minute each of serial reaction time (SRT), logical reasoning task (LRT), serial subtraction task (SUB) tests.

The SRT task displays a four key keypad with a different character or symbol on each key. One of the four graphics will be shown in a display area and the subject must click on the corresponding key as quickly as possible. Display characters are selected from the four-keypad characters randomly with replacement. Since this allows for sequential repetition of a character, the display colors are reversed from presentation to presentation so that the subject can detect the onset of a new stimulus (Pen SUSOPS Help File, 2008).

In the SUB test, the subject is presented with an initial subtraction problem. The subtrahend is in the range of 500-999, and the minuend is in the range 5-9. The subject continuously subtracts the fixed minuend from their most recent result, starting with an assigned subtrahend. The subject enters their answer by clicking on a numeric keypad or pressing the corresponding keys on the keyboard. No further input is accepted after the specified duration has elapsed (Pen SUSOPS Help File, 2008).

The LRT presents a series of problems concerning the relationship between two entities, A and B. A proposition is displayed in the form; entity relationship other-entity. Examples would be A precedes B, and B is not followed by A. The proposition is followed by a statement in the form "AB" or "BA" and the subject responds by clicking on either the TRUE or FALSE button. Propositions and statements are displayed concurrently. The task continues until the specified duration elapses (Pen SUSOPS Help File, 2008).

3.2.5 Subjective Quantification of Motion Sickness

Subjects reported symptoms of motion sickness based on the 7-point nausea rating scale (see Table 3.3) at regular, 2-minute intervals, which was reduced to 1-minute intervals as the subjects approached the defined experimental termination score of 6 or if the core body temperature approached 35°C. Subjects were also encouraged to report their symptoms (e.g. stomach awareness, nausea, headache). Participants also reported subjective drowsiness and cold comfort levels.

Subjects also reported pre- and post-motion symptoms according to Graybiel's Diagnostic Criteria for Grading the Severity of Acute Motion Sickness (Table 3.4). Symptoms pre-and post-motion exposures were graded using this scoring chart, which gave a quantitative value to symptoms based on their severity. The diagnostic tool for grading motion sickness severity is largely used by the investigator to evaluate the subject's motion sickness. Pallor and sweating (as observed by the investigator) and nausea (as reported by the subject) are allocated a severity score. Points are given for each symptom/severity reported or observed and the total Graybiel score is calculated. The final Graybiel score was the calculated difference between post- and pre-motion scores (Graybiel et al., 1968).

Table 3.3: The 7-point Nausea Rating Scale (Golding and Kerguelen, 1992)

Rating		Definition
0	.....	No Symptoms
1	.....	Any unpleasant symptoms, however slight
2	.....	Mild unpleasant symptoms (stomach awareness, sweating but no nausea)
3	.....	Mild nausea
4	.....	Mild to moderate nausea
5	.....	Moderate nausea but can continue
6	.....	Moderate nausea, want to stop

Table 3.4:Graybiel's diagnostic criteria for grading the severity of acute motion sickness. (Graybiel et al., 1968).

Category	Pathogonomic 16 Points	Major 8 Points	Minor 4 Points	Minimal 2 Points	QS 1 Point
Nausea Symptom	Vomiting / Retching	Nausea II/III	Nausea I	Epigastric Discomfort	Epigastric Awareness
Skin		Pallor III	Pallor II	Pallor I	Flushing/ Subjective Warmth/ Red Face
Cold Sweating		III	II	I	
Increased Salivation		III	II	I	
Drowsiness		III	II	I	
Pain					Persistent Headache
CNS					Dizziness- Eyes closed II, Eyes Open III

The original sources of the 7-Point Nausea Rating Scale (Golding and Kerguelen, 1992) and Graybiel's diagnostic criteria for grading the severity of acute motion sickness (Graybiel et al., 1968) did not report either reliability or validity coefficients for their respective scales. However, Graybiel et al. (1968) reported that reliability and validity of the diagnostic criteria was demonstrated by evaluating the effectiveness of anti-motion sickness drugs using a double-blind experimental technique.

3.2.6 Data Collection Protocol

The duration of each trial lasted approximately an hour and a half, including the preparation of subjects, baseline, and exposure to motion (lasting a maximum of one hour). The parameters being monitored and collected during this period were surface skin temperature, core body temperature, galvanic skin response, and psychomotor performance measures using the SUSOPS task battery and subjective nausea rating scores.

Figure 3.4 represents the timeline of events beginning with subject preparation, through baseline measurement, and the sequence of events corresponding to each data collection interval for each trial.

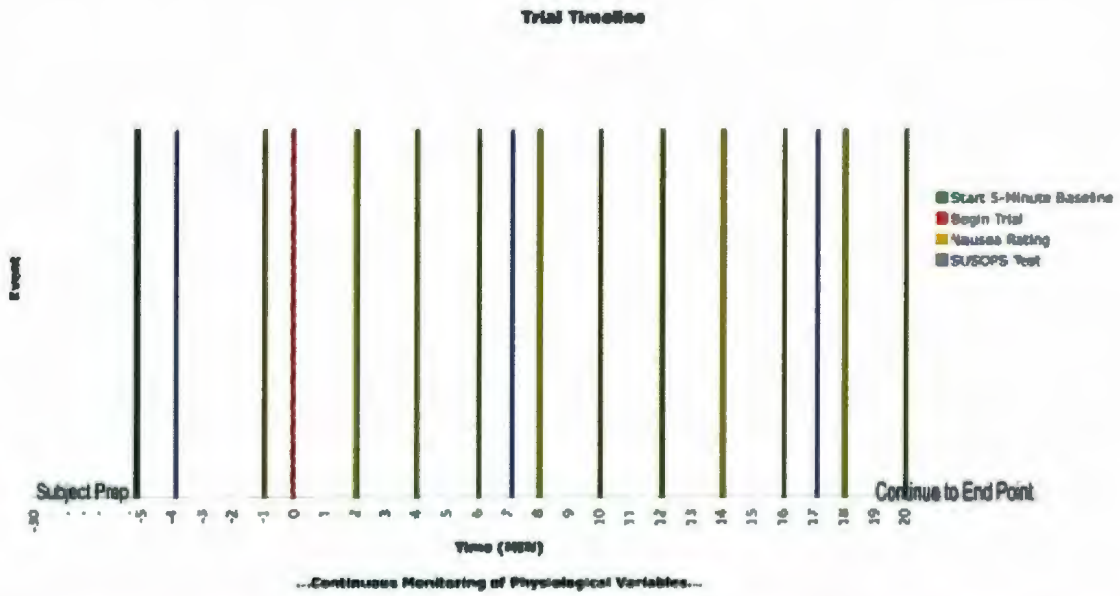

Figure 3.4: Timeline of events during trial. This timeline is subject dependent. Each endpoint was determined by voluntary withdrawal, determined by reaching a maximum nausea score (6), or completion of the 60-minute trial. The colours denote the variables collected at the indicated minute indicated on the x-axis.

3.3 Statistical Analysis

The perceptual, physiological and psychomotor data were analyzed by repeated measures ANOVA using SPSS (v11.0) software. This examined the difference in scores from the baseline (pre-motion) measure and the final (post-motion) recorded or reported score across the seven conditions (6 drugs and a placebo). A two-way ANOVA considering the effects of medication and time series was not employed because of the large variability in trial duration. That is, in some cases the subject may have gone the full 60-minutes of exposure or in some cases only lasted 14-minutes. Given the small sample-size and the methodological approach inherently creates opportunities for considerable data loss over time. A Tukey's LSD post hoc test was identified to be used if there were differences found between main factor effects.

4.0 RESULTS

4.1 Introduction

This chapter reports the results of the perceptual, physiological and psychomotor measures recorded during the experimental trials. Table 4.1 reports the total time of motion exposure and the maximum 7-point nausea rating score (in brackets) achieved by each subject for each experimental condition. Mean values are reported in subsequent sections that report the statistical analyses of these variables.

4.2 Results of Psychophysical Data Collection

Statistical analyses of the data collected during the experimental trials were conducted using a series one-way ANOVA. In all cases, no statistical differences were observed for the main effect medication. Reasons for not detecting significant difference are discussed later in the Discussion chapter. However, for archival purposes, the mean, standard deviation (SD) and coefficient of variation (CV) for each experimental variable are reported. Furthermore, the percent change from the value measured during the "placebo" trial is calculated for each parameter. Using this percent change value, the differences from the placebo were put in a rank order. This approach allows for a qualitative assessment for similarities between the different drug conditions. Graybiel et al. (1968) suggested that it was possible to rank the different drugs (or combination of drugs) by their relative effectiveness in order to determine whether there were trends in their principle pharmaceutical actions.

4.2.1 Duration of Trial

Statistical analysis of trial duration per treatment condition was tested using repeated measures ANOVA. The results of the ANOVA indicated there was no significant difference found between the trial duration of each treatment condition ($F_{6,12}$=0.815;p=0.590). These data are reported in Table 4.2.

Table 4.1 Trial duration in minutes and 7-point nausea rating score (in brackets) per subject and drug treatment.

SUBJECT/ DRUG	PLACEBO	PROM+CAF	MEC	DIM	CHL	SCOP+DEX	PROM+DEX
1	23 (6)	16(6)	20 (6)	35 (6)	22 (6)	60 (3)	60 (0)
2	60 (4)	60 (0)	60 (4)	60 (3)	60 (1)	60 (0)	60 (2)
3	60 (3.5)	60 (2.5)	60 (3)	60 (3)	60 (2)	60 (2.5)	60 (2)
4	39 (6)	14 (6)	60 (2)	44 (6)	60 (5.5)	60 (0)	29 (6)
5	60 (5)	60 (5)	60 (3)	60 (4)	60 (5)	60 (4)	50 (6)
6	60 (4)	60 (5)	60 (2)	60 (1)	60 (1)	60 (3)	60 (1)
7	52 (6)	60 (2)	60 (2)	60 (0)	60 (2)	60 (2)	60 (2)
8	22 (6)	60 (0)	22 (6)	20 (6)	60 (1)	18 (6)	60 (5)
9	51 (6)	60 (5)	60 (4)	60 (5.5)	48 (6)	43 (6)	60 (4)
10	56 (6)	60 (5)	60 (3)	60 (2)	60 (4)	60 (3)	60 (5.5)
11	60 (5.5)	60 (1)	60 (5.5)	46 (6)	45 (6)	60 (0)	37 (6)
12	33 (6)	43 (6)	25 (6)	60 (5.5)	38 (6)	36 (6)	60 (5)
13	60 (5)	60 (4)	60 (3.5)	60 (1.5)	60 (5)	60 (3)	60 (3)

Table 4.2: Trial duration by treatment.

	Mean (min)	SD (min)	CV (%)	% Change from Placebo	RANK
Placebo	***48.95***	***14.62***	***29.87***		
Prom + Caf	50.94	16.96	33.29	4.07	6
Mec	51.29	16.59	32.35	4.78	5
Dim	52.78	12.66	23.99	7.82	4
Chl	53.28	12.01	22.54	8.85	3
Scop + Dex	53.61	13.22	24.66	9.52	2
Prom + Dex	55.85	10.29	18.42	14.10	1

4.2.2 Subjective Rating of Symptoms of Motion Sickness

4.2.2.1 7-Point Nausea Rating

A repeated measures ANOVA was used to test the highest subjective rating based on the Golding-Kergeulen 7-Point nausea rating scale per treatment (refer to Table 3.3). The results of the ANOVA indicated there was a significant difference ($F_{6,12}$=4.533;p=.034). The mean scale score of the Placebo trial was significantly different from all other treatment conditions. These data are reported in Table 4.3.

Table 4.3: 7-point nausea rating scale scores by treatment.

	Mean (NR)	SD (NR)	CV (%)	% Change from Placebo	RANK
Placebo	***5.31***	***0.93***	***17.42***		
Prom + Caf	3.65	2.27	62.11	-31.26	2
Mec	3.85	1.56	40.52	-27.50	5
Dim	3.81	2.19	57.35	-28.25	4
Chl	3.88	2.14	55.21	-26.93	6
Scop + Dex	2.96	2.17	73.14	-44.26	1
Prom + Dex	3.65	2.10	57.40	-31.26	2

4.2.2.2 Graybiel Score of Motion Sickness

Pre- and post-motion Graybiel Scores were collected from each participant for each trial (refer to Table 3.4). Results from the ANOVA indicated there were no change in the difference scores across drug treatments ($F_{6,12}$=1.428;p=.324). These data are reported in Table 4.4.

Table 4.4: Mean Graybiel scores by treatment.

	Mean	SD	CV	% Change from Placebo	RANK
Placebo	***9.15***	***4.51***	***49.25***		
Prom + Caf	6.15	4.41	71.76	-32.79	2
Mec	8.00	4.85	60.60	-12.57	6
Dim	7.08	5.52	77.90	-22.62	3
Chl	7.08	4.96	70.03	-22.62	3
Scop + Dex	4.69	4.15	88.51	-48.74	1
Prom + Dex	7.15	5.06	70.83	-21.86	5

Results of the Graybiel scores normalized to the trial duration per treatment are presented in Table 4.4. The ANOVA reported no significant difference between the normalized scores ($F_{6,12}$=1.156;p=.422).

Table 4.5: Graybiel scores normalized to trial duration by treatment.

	Mean	SD	CV	% Change from Placebo	RANK
Placebo	***0.23***	***0.16***	***69.57***		
Prom + Caf	0.18	0.23	127.78	-21.74	4
Mec	0.23	0.27	117.39	0.00	6
Dim	0.18	0.20	111.11	-21.74	4
Chl	0.16	0.15	93.75	-30.43	3
Scop + Dex	0.12	0.16	133.33	-47.83	1
Prom + Dex	0.15	0.14	93.33	-34.78	2

4.3 Physiological Parameters

Physiological parameters were analyzed for 2 distinct periods, the no-motion baseline and the subsequent simulator motion periods. The mean value for the last minute of each of these periods was calculated and tested for significance.

4.3.1 Core Temperature

Core temperatures were collected during baseline period for each trial. Statistical analysis revealed no differences between the core temperature per treatment during baseline ($F_{6,12}$=0.655;p=.689). These data are reported in Table 4.6.

Table 4.6: Baseline core temperature by treatment.

	Mean (°C)	SD (°C)	CV (%)	% Change from Placebo	RANK
Placebo	***38.34***	***1.53***	***3.98***		
Prom + Caf	37.78	0.96	2.55	-1.45	2
Mec	38.21	1.05	2.75	-0.35	4
Dim	38.41	1.36	3.53	0.18	5
Chl	37.16	0.42	1.13	-3.07	6
Scop + Dex	38.27	1.20	3.14	-0.19	3
Prom + Dex	38.75	1.13	2.92	1.07	1

The ANOVA indicated no significant difference between core temperatures at the time of termination of the trial ($F_{6,12}$=0.573;p=.743). Data are reported in Table 4.7.

Table 4.7: Trial core temperature by treatment.

	Mean (°C)	SD (°C)	CV (%)	% Change from Placebo	RANK
Placebo	***37.87***	***1.51***	***3.99***		
Prom + Caf	37.71	1.08	2.86	-0.42	5
Mec	38.02	1.05	2.76	0.40	4
Dim	38.41	1.45	3.79	1.42	2
Chl	36.98	0.73	1.97	-2.35	6
Scop + Dex	38.23	1.16	3.02	0.96	3
Prom + Dex	38.64	1.17	3.03	2.04	1

The difference between the core temperature at point of motion termination and the baseline core temperature was calculated and tested using an ANOVA. The results of the ANOVA reported no significant change in the difference scores across treatments ($F_{6,12}$=0.872;p=.558). These data are reported in Table 4.8.

Table 4.8: Difference between end of trial and baseline core temperature by treatment.

	Mean (°C)	SD (°C)	CV (%)	% Change from Placebo	RANK
Placebo	***-0.47***	***0.89***	***190.58***		
Prom + Caf	-0.07	0.21	300.02	-84.75	4
Mec	-0.19	0.12	66.81	-60.06	1
Dim	0.00	0.31	593.89	-100.08	6
Chl	-0.18	0.55	300.91	-60.74	2
Scop + Dex	-0.03	0.14	402.43	-92.57	5
Prom + Dex	-0.11	0.50	454.35	-76.52	3

4.3.2 Skin Temperature

The mean skin temperature was calculated using a weighting equation developed by Hardy and Dubois (1938). The ANOVA reported no significant differences in mean skin temperatures between treatments at baseline ($F_{6,12}$=0.992;p=.510). These data are reported in Table 4.9.

Table 4.9: Baseline skin temperature by treatment.

	Mean (°C)	SD (°C)	CV (%)	% Change from Placebo	RANK
Placebo	***27.77***	***2.17***	***7.81***		
Prom + Caf	28.36	1.37	4.83	2.12	5
Mec	28.1	2.14	7.62	1.19	3
Dim	28.43	1.83	6.44	2.38	6
Chl	28.26	2.07	7.32	1.76	4
Scop + Dex	27.31	1.97	7.21	-1.66	2
Prom + Dex	27.28	2.51	9.20	-1.76	1

The weighted mean skin temperature during the last minute of the motion exposure period was tested using a one-way ANOVA. The statistical test reported no significant difference ($F_{6,12}$=2.030;p=.188). These data are reported in Table 4.10.

Table 4.10: Trial skin temperature by treatment.

	Mean (°C)	SD (°C)	CV (%)	% Change from Placebo	RANK
Placebo	***26.13***	***2.25***	***8.61***		
Prom + Caf	26.89	1.60	5.95	2.91	6
Mec	26.7	1.97	7.38	2.18	5
Dim	26.39	2.14	8.11	1.00	4
Chl	25.76	2.21	8.58	-1.42	3
Scop + Dex	25.59	2.40	9.38	-2.07	2
Prom + Dex	25.06	2.54	10.14	-4.09	1

The difference between end of the motion exposure period and baseline weighted mean skin temperature was calculated and tested by an ANOVA. There was no significant difference reported ($F_{6,12}$=2.237;p=.158). These data are reported in Table 4.11.

Table 4.11: Difference between trial end and baseline skin temperature by treatment.

	Mean (°C)	SD (°C)	CV (%)	% Change from Placebo	RANK
Placebo	***-1.64***	***0.90***	***54.88***		
Prom + Caf	-1.47	0.77	*52.38*	10.37	5
Mec	-1.4	0.95	*67.86*	14.63	6
Dim	-2.03	0.67	*33.00*	23.78	3
Chl	-2.51	1.22	*48.61*	53.05	1
Scop + Dex	-1.73	1.41	*81.50*	5.49	4
Prom + Dex	-2.22	0.89	*40.09*	35.37	2

Skin temperatures, normalized to trial duration, between treatments were tested using an ANOVA ($F_{6,12}$=3.456;p=.065). These data are presented in Table 4.12.

Table 4.12: Mean normalized skin temperature by treatment.

Table 4.11	Mean (°C/min)	SD (°C/min)	CV (%)	% Change from Placebo	RANK
Placebo	***-0.04***	***0.02***	***50.00***		
Prom + Caf	-0.03	0.01	*33.33*	-25.00	3
Mec	-0.03	0.02	*66.67*	-25.00	3
Dim	-0.04	0.02	*50.00*	0.00	2
Chl	-0.05	0.02	*40.00*	25.00	1
Scop + Dex	-0.03	0.02	*66.67*	-25.00	3
Prom + Dex	-0.04	0.01	*25.00*	0.00	2

4.3.3 Galvanic Skin Response

Galvanic Skin Response data were collected and analyzed. Results were inconclusive, due to the fact that the data were likely corrupted because the GSR unit was employed in an air-conditioned cabin. Subjects complained of finger numbness caused by the coldness of the metal fingertip electrodes. The investigator assured that the numbness was not due to an inappropriately applied finger strap.

4.3 SUSOPS Scores

SUSOPS tests were performed during the first 3 minutes of baseline and at ten-minute intervals during each trial, starting at the 7th minute of motion exposure (See Figure 3.4). Statistical analysis of these data compares effect of the drug on each SUSOPS test

measurement interval (eg: SUSOPS scores during the placebo condition at baseline, at time 1, etc).

4.3.1 Logical Reasoning Task (LRT)

4.3.1.1 LRT Response Time

LRT average response times were collected for each trial. A repeated measures ANOVA was conducted to analyze the response time scores. The statistical test reported no significant differences between the SUSOPS measurement intervals for each drug treatment ($F_{6,12}$=2.254;p=.482). Data are reported in Table 4.13.

Table 4.13: LRT average response time.

Drug	Time	Mean (ms)	Std. Error	CV	% Change from Placebo
PLACEBO	Baseline	4319.18	649.04	15.03	
	Final	3757.34	279.29	7.43	13.01
MEC	Baseline	3606.80	451.60	12.52	
	Final	3538.57	357.83	10.11	1.89
CHL	Baseline	3511.36	265.91	7.57	
	Final	3725.46	317.52	8.52	6.10
DIM	Baseline	3619.89	382.91	10.58	
	Final	4211.81	760.65	18.06	16.35
PROM + DEX.	Baseline	3995.94	497.80	12.46	
	Final	3670.11	240.20	6.54	8.15
PROM + CAF.	Baseline	3794.80	347.00	9.14	
	Final	3833.99	297.55	7.76	1.03
SCOP + DEX.	Baseline	3383.47	259.93	7.68	
	Final	3393.32	319.43	9.41	0.29

4.3.1.2 LRT Frequency and Accuracy

An ANOVA was used to analyze the response frequency (number of attempts) of the LRT task. No significant differences were found between the SUSOPS measurement intervals for each drug treatment ($F_{6,12}$=1.299;p=.602). The data are reported in Table 4.15.

Table 4.14: LRT response frequency.

Drug	Time	Mean	Std. Error	CV	% Change from Placebo
PLACEBO	Baseline	15.00	1.65	11.02	
	Final	15.69	1.32	8.40	4.62
MEC	Baseline	17.08	1.58	9.25	
	Final	17.42	1.62	9.32	1.99
CHL	Baseline	17.00	1.33	7.80	
	Final	16.15	1.37	8.46	-4.98
DIM	Baseline	17.15	1.75	10.18	
	Final	15.77	1.89	12.00	8.07
PROM + DEX.	Baseline	15.31	1.21	7.88	
	Final	15.54	1.13	7.27	1.51
PROM + CAF.	Baseline	15.85	1.44	9.12	
	Final	15.09	1.43	9.50	4.77
SCOP + DEX	Baseline	18.31	1.42	7.76	
	Final	18.25	1.59	8.73	0.32

The number of correct responses in each trial was calculated and tested by an ANOVA. The statistical test reported no significant differences between the SUSOPS measurement intervals for each drug treatment ($F_{6,12}$=.607;p=.776). The data are reported in Table 4.16.

Table 4.15: LRT correct responses.

Drug	Time	Mean	Std. Error	CV	% Change from Placebo
PLACEBO	Baseline	0.78	0.07	9.54	
	Final	0.84	0.05	6.54	6.85
MEC	Baseline	0.84	0.04	5.29	
	Final	0.88	0.06	7.23	4.76
CHL	Baseline	0.93	0.03	3.35	
	Final	0.92	0.03	3.18	1.32
DIM	Baseline	0.89	0.05	5.78	
	Final	0.91	0.04	3.95	1.82
PROM + DEX.	Baseline	0.87	0.05	5.69	
	Final	0.88	0.04	4.46	1.82
PROM + CAF.	Baseline	0.86	0.06	6.87	
	Final	0.96	0.02	2.36	11.58
SCOP + DEX.	Baseline	0.85	0.06	6.59	
	Final	0.93	0.03	3.21	8.57

4.3.2 Serial Subtraction Task (SUB)

4.3.2.1 SUB Response Time

A repeated measure ANOVA was used to test the SUB task response time scores. No significant differences were found between the SUSOPS measurement intervals for each drug treatment ($F_{6,12}$=.445;p=.840). The data are reported in Table 4.17.

Table 4.16: SUB average response time.

Drug	Time	Mean (ms)	Std. Error	CV	% Change from Baseline
PLACEBO	Baseline	5737.21	772.24	13.46	
	Final	6060.72	848.70	14.00	5.64
MEC	Baseline	5004.63	673.77	13.46	
	Final	5157.19	445.81	8.64	3.05
CHL	Baseline	7490.04	1148.87	15.34	
	Final	6928.81	1110.78	16.03	7.49
DIM	Baseline	5829.93	908.02	15.58	
	Final	5869.88	868.07	14.79	0.69
PROM + DEX.	Baseline	5473.59	722.67	13.20	
	Final	5596.15	722.65	12.91	2.24
PROM + CAF.	Baseline	4967.09	563.71	11.35	
	Final	5665.17	898.98	15.87	14.05
SCOP + DEX.	Baseline	5486.57	695.94	12.68	
	Final	5033.08	472.87	9.40	8.27

4.3.2.2 SUB Frequency and Accuracy

A one-way repeated measures ANOVA was used to statistically analyze the frequency of response data. The statistical test reported no significant differences between the SUSOPS measurement intervals for each drug treatment ($F_{6,12}$=.615;p=.773). The data are reported in Table 4.19.

Table 4.17: SUB frequency of response.

Drug	Time	Mean (# responses)	Std. Error	CV	% Change from Baseline
PLACEBO	Baseline	12.08	1.63	13.50	
	Final	11.54	1.71	14.84	4.46
MEC	Baseline	13.85	1.54	11.12	
	Final	12.83	1.33	10.36	7.31
CHL	Baseline	10.23	1.17	11.46	
	Final	10.77	1.74	16.19	5.26
DIM	Baseline	11.23	1.65	14.72	
	Final	12.00	1.54	12.80	6.85
PROM + DEX.	Baseline	13.38	1.95	14.57	
	Final	11.69	1.36	11.64	12.65
PROM + CAF.	Baseline	12.77	1.61	12.58	
	Final	13.00	1.52	11.72	1.81
SCOP + DEX.	Baseline	11.77	1.66	14.11	
	Final	11.92	1.05	8.78	1.31

Analysis of the correct responses from the SUB tasks by ANOVA reported no significant differences between the SUSOPS measurement intervals for each drug treatment ($F_{6,12}$=3.160;p=.416). The data are reported in Table 4.20.

Table 4.18:SUB correct responses

Drug	Time	Mean	Std. Error	CV	% Change from Baseline
PLACEBO	Baseline	0.71	0.11	14.84	
	Final	0.75	0.08	11.15	5.21
MEC	Baseline	0.53	0.13	23.77	
	Final	0.53	0.11	20.87	0.39
CHL	Baseline	0.78	0.09	11.46	
	Final	0.45	0.11	24.52	42.50
DIM	Baseline	0.69	0.11	15.84	
	Final	0.50	0.11	22.80	28.34
PROM + DEX.	Baseline	0.58	0.11	19.19	
	Final	0.48	0.11	21.91	17.03
PROM + CAF.	Baseline	0.78	0.09	11.64	
	Final	0.64	0.10	15.31	17.56
SCOP + DEX.	Baseline	0.51	0.11	21.56	
	Final	0.70	0.10	14.75	37.77

4.3.3 Serial Reaction Time (SRT)

4.3.3.1 SRT Reaction Time

The one-way repeated measures ANOVA analysis of the average reaction time during the SRT task reported no significant differences between the SUSOPS measurement intervals for each drug treatment ($F_{6,12}$=.260;p=.926). The data are reported in Table 4.21.

Table 4.19: SRT average reaction time.

Drug	Time	Mean (ms)	Std. Error	CV	% Change from Baseline
PLACEBO	Baseline	697.64	32.86	4.71	
	Final	742.20	52.87	7.12	6.39
MEC	Baseline	679.26	35.73	5.26	
	Final	668.15	29.16	4.36	1.64
CHL	Baseline	660.94	19.60	2.96	
	Final	682.50	23.66	3.47	3.26
DIM	Baseline	656.74	24.16	3.68	
	Final	717.57	41.08	5.73	9.26
PROM + DEX.	Baseline	672.17	26.55	3.95	
	Final	688.31	22.10	3.21	2.40
PROM + CAF.	Baseline	657.72	24.46	3.72	
	Final	698.58	31.53	4.51	6.21
SCOP + DEX.	Baseline	672.58	29.69	4.41	
	Final	662.80	25.58	3.86	1.45

4.3.3.2 SRT Frequency and Accuracy

Frequency scores of the SRT task were tested using an ANOVA. The statistical test reported no significant differences between the SUSOPS measurement intervals for each drug treatment ($F_{6,12}$=082;p=.996). The data are reported in Table 4.23.

Table 4.20: SRT frequency scores.

Drug	Time	Mean	Std. Error	CV	% Change from Baseline
PLACEBO	Baseline	73.62	2.75	3.74	
	Final	69.77	3.25	4.66	5.22
MEC	Baseline	76.15	2.82	3.71	
	Final	75.58	2.80	3.71	0.75
CHL	Baseline	76.38	1.94	2.54	
	Final	72.69	2.14	2.94	4.83
DIM	Baseline	76.23	2.45	3.21	
	Final	72.08	3.37	4.67	5.45
PROM + DEX.	Baseline	75.08	2.55	3.39	
	Final	72.62	1.87	2.58	3.28
PROM + CAF.	Baseline	77.23	2.88	3.73	
	Final	71.82	2.61	3.64	7.01
SCOP + DEX.	Baseline	76.15	2.33	3.06	
	Final	75.33	2.34	3.10	1.08

Statistical analysis comparing the correct responses on the SRT task reported no significant differences between the SUSOPS measurement intervals for each drug treatment ($F_{6,12}$ =1.853;p=.523). The data are reported in Table 4.24.

Table 4.21: SRT correct responses

Drug	Time	Mean	Std. Error	CV	% Change from Baseline
PLACEBO	Baseline	0.99	0.00	0.23	
	Final	0.99	0.00	0.32	0.08
MEC	Baseline	1.00	0.00	0.17	
	Final	0.99	0.00	0.26	0.44
CHL	Baseline	0.99	0.00	0.24	
	Final	0.99	0.00	0.32	0.12
DIM	Baseline	0.99	0.00	0.34	
	Final	0.99	0.01	0.52	0.37
PROM + DEX.	Baseline	1.00	0.00	0.24	
	Final	0.99	0.00	0.36	0.53
PROM + CAF.	Baseline	0.99	0.00	0.26	
	Final	0.99	0.00	0.39	0.61
SCOP + DEX.	Baseline	1.00	0.00	0.15	
	Final	0.99	0.00	0.26	0.57

5.0 DISCUSSION

5.1 Introduction

This research evaluated a range of drugs belonging to different pharmacological classes that are known to show varying degrees of effectiveness for symptom remediation among individuals who are susceptible to motion sickness. All anti-motion sickness drugs employed in this study are available for use with prescriptions and they belong to the following pharmacological classes: antihistamines, anticholinergics and antiemetics (Personal Communication, Dr. Bob Cheung).

The interpretation of these data are based on subject responses and, discussion of pharmacokinetic outcomes are beyond the scope of this analysis. Implications of the findings of this work will provide guidance to persons working in motion rich environments who cannot afford to lose vigilance or physical capacity while performing their job.

Statistical analysis reported non-significant differences between the drugs on each of the variables tested. This lack of significance may be attributed to the small sample size (n=13), a potential habituation to motion (despite a one-week washout between trials) and all drug interventions, except for the placebo, have known, documented mediating effects for motion sickness, thus, from the onset, minimizing any potential to detect inter-trial differences.

A lack of statistical significance does not translate into a lack of important findings. While not statistically significant, there were similarities in the placebo trial compared to the trials where drugs were ingested. While one may not anticipate measureable differences between the trials where drugs were used, it was expected that these would be different to the placebo trial.

While, in most cases, no significant differences were detected, the data were further scrutinized using a ranking approach. This qualitative approach was considered to assess whether there were similarities between the drug effects and the placebo condition. In this respect, the drugs could be evaluated in terms of relative effectiveness on physiological parameters, psychomotor performance, and psychophysical reports of motion sickness.

5.2 Duration of Trial

The duration of the trials varied based on three criteria that determined end-point. Subjective nausea rating reached six (voluntary withdrawal), the trial terminated at 60 minutes, or core body temperature reached 35°C. There were no instances where a participant was required to terminate due to loss of core body temperature to 35°C. Thus, trial duration was determined by the participant's tolerance to the motion exposure.

As anticipated, the Placebo trials were terminated earliest. Prom + Dex and Scop + Dex were ranked number one and two respectively, with the two greatest percent change from placebo (Table 4.2). A study by Wood and Graybiel (1968) evaluated 16 formulations of anti-motion sickness drug formulations in the Pensacola Slow Rotation room and required the participants to perform head movements to elicit a provocative sensory conflict. Scopolamine + Amphetamine were tested in various dosages in combination and alone. No formulations were the same as employed in this study, however, it was found that the combination of the two increased tolerance to provocative motion by almost 200% over the average number of head movements during placebo trials. Wood et al. (1965) reported similar findings using the same protocol to test the ability of a selection of drugs to mediate motion sickness development. Oral Scopolamine was again validated as a successful treatment for motion sickness prevention in a study by Graybiel et al. (1976), which ranked second to Promethazine + Ephedrine. As reported in the study by Wood and Graybiel (1968) the addition of a stimulant may increase tolerance to provocative motion as it reduces the drowsiness effect of the drug. While in some past studies the

addition of a stimulant improved motion tolerance and performance, the anecdotal data collected during these trials indicated some of the participants felt increased anxiety and nervousness, which reduced their comfort during the motion exposure.

5.3 Subjective Rating of Symptoms of Motion Sickness

It was expected that the six drugs employed in this study would have a positive improvement on the subject's tolerance to motion exposure. The 7-Point Nausea Rating scale and Graybiel Score were the criteria used to measure motion sickness symptom development. Drug intervention would be expected to ameliorate symptom development or prevent the onset of motion sickness, thus increasing trial duration. Overall, Scop + Dex and Prom + Caf were ranked one and two respectively (see Tables 4.2, 4.3, 4.4 and 4.5) as most effective in preventing or mediating the development of motion sickness symptoms, Prom + Dex ranked third best at mediating symptoms of motion sickness.

The results of the subjective rating of motion sickness symptoms data are very similar to those of the trial duration, as they reflect the ability of the drugs to mediate motion sickness symptoms and improve subject's tolerance to provocative motion. Promethazine and Scopolamine with the addition of a stimulant prove in this study to best mediate symptom development and experience.

5.4 Physiological Measures

5.4.1Core Temperature

The range of core temperatures seemed to be quite varied and perhaps not within expected physiological ranges. While this may be due to the ingestion of the pharmaceuticals, this variability may be a result of equipment calibration issues. This variability will likely influence the results of the statistical analyses.

The subject's core body temperature was not significantly affected by the exposure to cold as the stimulus was 10°C and the exposure was of variable duration, from 20-60 minutes, and likely not strong enough to elicit a decrement in core body temperature. This was reflected in the statistical analysis. No statistical differences were revealed, however, there may have been practical differences between the treatment conditions, Prom + Dex and Mec were ranked one and two respectively (see Tables 4.6, 4.7 and 4.8) as most effective in preserving core body temperature. For the purpose of recommending these drugs to individuals who are in occupations that require them to be exposed to extreme temperatures, Prom + Dex should be recommended with caution as Promethazine affects thermoregulation (Canadian Pharmaceuticals Association, 2007). The concept that a drug intervention might affect or facilitate the cooling of motion sickness sufferers who are exposed to cold environments while developing or suffering from motion sickness is novel. There have been reports of motion sickness having a potentiating effect upon individual cooling during immersion in water post-motion sickness provocation (Mekjavic et al., 2001). Findings were similar in two separate protocols that provoked motion sickness using a human centrifuge and immersing subjects in a 28°C bath (Mekjavic et al., 2001), and a protocol that provoked motion sickness using a rotation chair and immersion in a 15°C bath (Nobel et al., 2003). Each experiment required the subjects take a 10-minute rest between motion sickness provocation and immersion. Each study reported significant decreases in core temperature in the immersion trials compared to the control trials. The present study varies in that the cold stimulus is less potent, as water conducts heat from the body at twenty three times the rate of air (Smith and Hanna, 1975). While the change in core temperature found in this study is not significant, given a stronger cold stimulus subjects may be at risk of greater heat loss during motion sickness development.

5.4.2 Skin Temperature

Similar to the core temperatures, the variability of these measurements is larger than expected. As explained above this may be due to equipment calibration issues,

physiological response to the ingested pharmaceuticals or exposure to the cold cabin temperatures.

Skin temperature was expected to decrease as the subjects were wearing sparse clothing, and the cabin temperature (10°C) was cold enough to elicit a peripheral vasomotor response. Prom + Dex and Chl were ranked one and two overall respectively (see Tables 4.9-4.12) as with these treatments subjects maintained higher surface skin temperatures. Scop + Dex was ranked as third most effective in preserving skin temperature.

There is little research that explores the effect of motion sickness on skin temperature in cold environments. A study by Barcroft and Edholm (1946) that evaluated forearm and calf cooling in air and water supports that prolonged exposures to air temperatures of under 20°C will result in skin cooling at increased rates at lower temperatures. A study by Cheung and Hofer (2001) reported increased blood flow to the forearm when subjects were exposed to Coriolis stimulation. The effect of increased peripheral blood flow elicited by provocative motion coupled with a cold environment may result in more rapid skin cooling. Drug interventions that mediate motion sickness symptoms may aide in the preservation of skin temperature; however, in a cold environment peripheral blood flow may be reduced when motion sickness symptoms are mediated. Skin temperature may decrease more, or at a faster rate in a cold environment as peripheral vasoconstriction would occur to preserve core temperature. In conditions where peripheral blood flow remains elevated it could be expected that motion sickness symptoms are stronger, and thus symptomatic sweating would result in skin temperatures remaining elevated and well perfused.

5.5 Psychomotor Measures

5.5.1 Cognitive Measures

The drugs all had the effect of drowsiness; however, those with dexamphetamine or caffeine added to the formulation to counteract the drowsiness effect were expected to

improve performance during the psychomotor tasks. Motion sickness and performance have been shown to have a negative relationship in past research (Comperatore and Rivera, 1998). Studies have also suggested that task performance during motion may improve tolerance to motion (Bos et al., 2005).

This study employed a SUSOPS task battery to measure how motion sickness stress affected logical reasoning, reaction/response time and basic math aspects of cognitive function, and how treatment conditions affected the same aspects of cognitive abilityChl and Scop + Dex ranked as the best overall as they resulted in the best performance on the SUSOPS tasks, and Prom + Caf was ranked second best overall performance on the SUSOPS task battery.

5.5.2 Reaction Time

The most sensitive reaction/response time task was the SRT. The number of responses elicited (see Table 4.23) and the response time (see Table 4.21 and 4.22) were the highest of the three SUSOPS tasks. There was over one response per second compared to the SUB and LRT tasks where response times were three seconds or more. The sensitivity of this measure allowed for a better indication of how reaction time was affected during each treatment condition. During each treatment condition reaction time between baseline and test one was negatively affected by the onset of motion. This was most apparent in the SRT task, and not so in the SUB and LRT as they both had much higher response times and had a higher degree of task difficulty. In the SRT task, typically administered as the final test for each treatment condition, reaction time was closer to that of baseline, most likely due to the subject becoming accustomed to the motion stimulus.

The effect of motion-induced interruptions on cognitive performance appears to be under-explored in the literature, and many performance decrements are largely studied, or attributed, as the result of motion sickness symptoms. Overall the drugs that most effectively preserved cognitive performance were Scop + Dex as the highest ranked and Prom + Caf and Mec ranking second. In the SRT task alone, which appeared to give a

better indication of reaction time due to the sensitivity of the response time, Prom + Caf ranked number one and Scop + Dex and Chl ranked second best.

5.5.3 Frequency and Accuracy

Response frequency may indicate the onset of motion sickness symptoms, or the difficulty of the task. In the SUB and LRT tasks there were far fewer responses elicited, and therefore in this case the task difficulty may be the cause. However, there was some variety in the frequency of responses across treatments, while not significant. Mec and Scop + Dex were the two drugs that saw the highest number of responses across all tests. This is the rank-order seen in the SRT response frequency chart as well (see Table 4.23).

The drugs that resulted in the highest response frequency were not in alignment with those drugs that elicited the highest number of correct responses. Chl, Prom + Caf and Placebo were ranked as the three best across all tests in accuracy. This might be due to the extreme drowsiness that was experienced on some of the other drugs, or the effect of the dexamphetamine stimulant in the Scopolamine and Promethazine. In the SRT trial Chl and Placebo were ranked as the first and second best in terms of accurate responses, however, in this test the responses across all drugs were all in the 98%, 99% and 100% correct range (see Table 4.24), thus the differences were very minor, and an inaccurate response in this test could be due to the motions of the waves and the actual physical effects of the motion on the participants ability to place the cursor in the correct position and click before being jolted by the ship motions. In both the SUB and the LRT correct responses (see Tables 4.20 and 4.16) Prom + Caf was ranked as one to the top two drugs in preserving accuracy in more challenging cognitive tasks. Perhaps in terms of accuracy, the LRT and SUB task are better representations of how the drugs affect the subjects' cognitive ability, as they are measuring basic arithmetic and logical reasoning.

6.0 CONCLUSIONS AND RECOMMENDATIONS:

The mediation of symptoms of motion sickness is critical in occupations requiring physical endurance and cognitive vigilance. Traditional pharmaceutical interventions will often induce fatigue and provoke other detrimental physiological, perceptual and psychomotor changes.

It was expected that any pharmaceutical intervention intended to mediate positively symptoms of motion sickness would have a beneficial effect on prevention of motion sickness symptom development and a concomitant positive effect on cognitive performance and physiological responses to the cold and motion stimuli.

After testing the four hypotheses and evaluating the effects of motion sickness and motion sickness medications on core body temperature, skin temperature and cognitive performance, the conclusion may be drawn that while there was no significant effect found, there were several outcomes that are important for many stakeholder groups. This section will discuss the drugs best suited to mitigate motion sickness based on the desirable or acceptable outcome of using anti-motion sickness to improve tolerance to the stimuli.

This research evaluated a range of drugs belonging to different pharmacological classes that are known to mediate symptoms of individuals who are susceptible to motion sickness. These drug classes included antihistamines, anticholinergics and antiemetics and generally are available by prescription.

The purpose of this study was to evaluate the ability of each of the six drugs to improve the tolerance of susceptible individuals to provocative motions and to assess which drug formulations least altered subject's perception, psychomotor and physiological performance. Findings of this work will provide guidance to persons working in motion

rich environments who cannot afford to lose vigilance or physical capacity while performing their job.

Statistical analysis reported non-significant differences between the drugs on each of the variables tested. This lack of significance may be attributed to the small sample size (n=13), a potential habituation to motion and that the subjects are being given drugs to prevent the development of motion sickness symptoms. However, the experimental design, by its nature, limited the likelihood of determining significant differences, specifically amongst the treatments that included anti-nauseant medications. In all cases, the trend was for the subject to demonstrate the most obvious signs of motion sickness under the placebo state.

Due to the lack of significance the data were analyzed using a rank-order approach. The percent change from the placebo condition was calculated for each drug for each variable. The larger positive percent change from placebo was ranked as the most "effective" drug. The drugs could then be evaluated in terms of effectiveness on physiological parameters, psychomotor performance, and psychophysical reports of motion sickness.

The treatment conditions influenced the various experimental measures differently, and thus, the results may be applied to specific scenarios, depending on the desired outcome of the drug intervention. Motion sickness symptoms were best mediated by **Scop + Dex and Prom + Caf**, and so would best be applied to scenarios where developing symptoms and side-effects from the treatment of motion sickness impairs decision-making ability..

Scop + Dex and Prom + Caf were also ranked in the top treatments for maintaining baseline cognitive ability under cold and motion stress, and **Scop + Dex** was also the best ranked drug for duration tolerance, so either of these treatments would be best applied in scenarios where motion sickness would impede vigilance and occupational performance, and prolonged exposure to the stimuli is required.

Prom + Dex, Mec and Chl best preserved skin and core temperatures, and **Prom + Dex** was also in the top three treatments that best mediated motions sickness symptoms, and duration tolerance. Therefore in these treatments would be best applied in scenarios where individuals are exposed to cold climates, however, it should be taken under advisement as Promethazine comes with a caution when used in extreme climates (Canadian Pharmaceuticals Association, 2007).

These data suggest that there are trends indicating some drugs are better used in some scenarios, such as those requiring cognitive awareness and optimal performance, while other drugs may be applied in situations where the main purpose is for the comfort of the passenger, or of someone whom vigilance and alertness is not required.

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Appendices

Appendix A Call for subjects Poster

[redacted]

Volunteers are needed for a study that will evaluate how body temperatures change with exposure to motion and anti-nausea medications.

- Contribute to our understanding of how people become sick due to motion.

Who can participate?

- Anyone between 19-55 years of age.
- Healthy individuals who are not on regular medications

Who cannot participate?

- Females currently pregnant
- Anyone with current heart or respiratory illnesses

To find out more, contact:

Elizabeth Coady – eacoady@mun.ca or 737-3138
Patricia Cumby – 778-0304 – Centre for Marine Simulation

Appendix B Consent To Take Part In Health Research

January 2006

Faculty of Medicine, Schools of Nursing and Pharmacy of Memorial University of Newfoundland; Eastern Health; Newfoundland Cancer Treatment and Research Foundation

CONSENT TO TAKE PART IN HEALTH RESEARCH

TITLE: The Effects of Motion Sickness

INVESTIGATOR(S): Dr. Scott N. MacKinnon

SPONSOR:

You have been invited to take part in a research study. It is up to you to decide whether to be in the study or not. Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This consent form explains the study.

The researchers will:

- **discuss the study with you**
- **answer your questions**
- **keep confidential any information which could identify you personally**
- **be available during the study to deal with problems and answer questions**

If you decide not to take part or to leave the study this will not affect your normal treatment.

1. Introduction/Background:

The main objective of this work is to investigate the effects of selected classes of anti-motion sickness drugs in suppressing motion sickness induced changes in body temperature.

Findings from this research will likely lead to insights about the mechanisms that mediates motion sickness severity and will generate guidance to better inform those who operate or train personnel who operate in cold and motion-rich environments.

2. Purpose of study:

The purpose of this study is to evaluate the effects of motion sickness on body temperature changes.

3. Description of the study procedures and tests:

Procedures that will be employed will include responding to questionnaires that will evaluate the individual's motion sickness susceptibility, reporting psycho-physical responses to the motion stimulus. The participant will be subjected to provocative motion, required to ingest an anti-motion sickness drug, or placebo. Temperature instrumentation a heart rate monitoring system, including ECG, and an electrodermal response system will be utilized to monitor the physiological responses of the participant to ensure their safety during the trials.

4. Length of time:

The participants will be expected to participate in 5 trials over a five week period. The trials will last approximately 1-2 hours each.

5. Possible risks and discomforts:

- Insertion of the rectal probe
- Motion sickness Symptoms (ie: headache, nausea, vomiting)
- Drowsiness, due to anti-motion medications
- Cold

6. Benefits:

It is not known whether this study will benefit you.

7. Liability statement:

Signing this form gives us your consent to be in this study. It tells us that you understand the information about the research study. When you sign this form, you do

not give up your legal rights. Researchers or agencies involved in this research study still have their legal and professional responsibilities.

8. **Confidentiality:**

   Participant's identity will be kept confidential. The results will be coded, and names will not be associated with trials, drugs or measurements taken.

9. **Questions:**

   If you have any questions about taking part in this study, you can meet with the investigator who is in charge of the study at this institution. That person is:

Dr. Scott N. MacKinnon ph:(709) 777-8746 or Elizabeth Coady, ph: 737-3138

Or you can talk to someone who is not involved with the study at all, but can advise you on your rights as a participant in a research study. This person can be reached through:

Office of the Human Investigation Committee (HIC) at 709-777-6974
Email: hic@mun.ca

Signature Page

Study title:

Name of principal investigator:

To be filled out and signed by the participant:

	Please check as appropriate:
I have read the consent [and information sheet].	Yes { } No { }
I have had the opportunity to ask questions/to discuss this study.	Yes { } No { }
I have received satisfactory answers to all of my questions.	Yes { } No { }
I have received enough information about the study.	Yes { } No { }
I have spoken to Dr. _____ and he/she has answered my questions	Yes { } No { }
I understand that I am free to withdraw from the study	Yes { } No { }

- at any time
- without having to give a reason
- without affecting my future care [student status, etc.]

I understand that it is my choice to be in the study and that I may not benefit. Yes { } No{}

I agree that the study doctor or investigator may read the parts of my hospital records which are relevant to the study. Yes { } No

I agree to take part in this study. Yes { } No { }

_____ _____

Signature of participant Date

_____ _____

Signature of witness Date

To be signed by the investigator:

I have explained this study to the best of my ability. I invited questions and gave answers. I believe that the participant fully understands what is involved in being in the study, any potential risks of the study and that he or she has freely chosen to be in the study.

_____ _____

Signature of investigator Date

Telephone number: _____

Appendix C Invasive Procedures Consent Form

Title: The effect of anti-motion sickness drugs, and physiological responses, in a cold and moving environment.

Rectal Probe: A small plastic tube is inserted through the anus into the rectum and is left indwelling for the experiment. Insertion of the probe may result in mild discomfort, but since the Subject inserts the probe themselves, this is minimal. Although there is a possible risk of perforation of the bowel during insertion (perhaps causing severe abdominal inflammation necessitating emergency surgery), the investigator and his associates are unaware of this ever having occurred.

I _____ hereby consent to the procedure above. These procedures and their complications have been explained to me to my satisfaction by the Investigator, and I have had the opportunity to ask questions both of the Investigator and of a physician.

Volunteer's Signature: _____ Date: _____
Witness Name: _____
Witness Signature: _____ Date: _____
Principal Investigator: _____ Signature: _____

Date: _____

I understand that I shall be given a copy of this consent form.

Appendix D Medical History Questionnaire

Experimental Medical Screening Questionnaire

Part 1: Personal Information

Surname:	Given Name:
Sex (Circle one): Male/Female	Date of Birth:
Phone #:	Address:

Part 2: Emergency Contact Information

Contact Name: Relationship to you:
Contact Number:

Part 3: Medical History

1. Please indicate whether you have now or have ever had a significant episode of one or more of the following:

Symptom	Have Now (√)	Have Had (√)	Symptom	Have Now (√)	Have Had (√)
Chest Pain/ Pressure			Leg cramps or pain		
Shortness of breath			Painful,swollen,stiff joints		
Irregular/Rapid heart beat			Weakness, numbness, tingling in extremities		
Weakness, dizziness, fainting			Weight loss or gain		
Wheezing			Difficulty sleeping		
Chronic Cough			Easily fatigued		
Spitting/Coughing up blood			Change in mood		
Hoarseness			Loss of memory		
Sore throat			Hallucinations		
Difficulty swallowing			Heat or cold intolerance		
Nausea/ Vomiting (motion sickness)			Heat related illness		
Frequent indigestion			Fever, chills, night sweats		
Abdominal cramps or pain			Frequent, severe, or persistent headaches		
Change in appetite or thirst			Persistent swollen glands		
Diarrhea or constipation			Change in vision (double vision)		
Change in appearance of stool			Eye Problems List which:		
Bleeding associated with bowel movement			Changes in hearing (hearing loss, ringing or roaring in the ears)		
Transient loss of coordination or of control of fine movement of hands			Ear problems List which:		

Transient confusion			Difficulty clearing ears or sinuses in an airplane		
Frequent or painful urination			New skin growths		
Incontinence			Change in color or shape of moles or warts		
Urinary discharge			Tendancy to bruise or bleed easily or to clot slowly		
Blood in urine			Tooth or gum problems List which:		
Neck or back pain					

2a. Indicate whether you have now or have had any of the following conditions:

Symptom	Have Now (√)	Have Had (√)	Symptom	Have Now (√)	Have Had (√)
Anaemia			Hernia		
Asthma			HIV/AIDS		
Bell's Palsy			Kidney/bladder disease (including stones)		
Claustrophobia			Pulmonary overpressure syndrome/air embolism		
Collapsed lung			Rheumatic fever		
Decompression sickness(Bends)			Speech, reading, learning disorder		
Gout			Suicide (thoughts or attempts)		
Head injury with unconsciousness or memory loss			Thyroid disease (goiter)		
Heart murmur			Tuberculosis or pleurisy		
Hepatitis (jaundice)			Ulcers		

2b. Have you suffered any significant injuries? Yes__ No__ (If no go to question 2c.)
If Yes indicate what type and approximate date(s):_____
_____

2c. Have you had any surgical procedures? Yes__ No__ (If no go to question 2d.)
If Yes indicate which procedures and approximate date(s): _____
_____

2d. Have you ever fractured a bone(s)? Yes__ No__ (If no go to Question 3.)
If Yes indicate which bone(s) and approximate date(s) _____
_____

3. Indicate whether you or a family member has or had the following conditions:

Condition	I have (√)	Someone in my family has/had (indicate relationship)	Additional Details
Diabetes			
High blood pressure			
Elevated blood cholesterol			

Heart problems			
Cancer or tumors			
Stroke			
Depression, Schizophrenia, other psychiatric problems			
Other significant diseases (indicate)			
Sudden death			
Epilepsy (seizures, fits, convulsions)			
Glaucoma			
Genetic disorders (indicate which)			

4. Have you ever given blood? Yes__ No__ (if No go to Question 5)
   If Yes what was the approximate date of your last donation? _____

5. Have you been treated in the past year for what you consider a significant condition?
   Yes__ No__ (If No go to Question 6)
   If Yes give details: _____

6. Do you have concerns about your fitness to participate in this experiment that you would like to discuss with a physician? Yes__ No__ (If no go to Part 4)
   If Yes specify: _____

Part 4: Personal Habits

1. Do you now or have you ever smoked?
   Never smoked __ (go to question 2)
   Current Smoker __ How many years? __ How many cigarettes do you smoke per day?
   Ex-smoker __ Year Quit? ____ How many cigarettes per day did you smoke? ___

2. Do you drink alcohol? Yes__ No__ (If no go to Question 3)
   If yes how many drinks per day? _____ -or- each week?_____

3a. Do you exercise regularly? Yes__ No__ (If no go to Question 3b.)
   If Yes what type of exercise have you done in the past week?
   How many minutes per day? _____ -or- Per Week? _____

3b. Do you have any factors that limit your exercise tolerance? Yes__ No__ (if no go to Question 3c.)
   If Yes explain. _____

3c. Do you regularly participate in one or more of the following extreme activities?

Activity	Yes (√)	No (√)

Scuba diving		
Flying		
Mountain climbing		
Motor car racing		
Skydiving		

4a. Are you taking any medication at this time (including vitamins and supplements)?
Yes__ No__ (if no go to question 4b.)
If Yes list: _____

4b. Have you stopped taking any medication in the last 30 days (including vitamins and herbal supplements)? Yes__ No__ (If No go to question 4c.)
If Yes list: _____

4c. Are you allergic to any medication? Yes__ No__ (If No go to question 5)
If Yes list: _____

5. Do you wear contact lenses? Yes__ No__

6. Are you color blind? Yes__ No__

7. Have you had corrective eye surgery? (LASIK/PRK)? Yes__ No__

Part 5: For Female Subjects Only

Section 1:

1a. Are you pregnant? Yes__ No__

2. Is there a possibility you could be pregnant? Yes__ No__
Indicate why: _____
(If there is a possibility you could be pregnant see your physician before continuing)

3. What was the first day of your last menstrual period? _____
Was this period normal for you (duration, flow, etc)? Yes__ No__
What is the length of your cycle? ____ days.
Is your cycle regular? Yes__ No__

4. Do you have any significant gynecological problems? Yes__ No__
If yes provide details: _____

4. Are you currently breastfeeding? Yes __ No__

Appendix E Motion Sickness Susceptibility Questionnaire

This questionnaire is designed to find out how susceptible to motion sickness you are and what sorts of motion are most effective in causing that sickness. Sickness here means feeling queasy or nauseated or actually vomiting. After some background questions, the questionnaire consists of two sections:
Section A is concerned with your **childhood** experiences of travel and motion sickness, that is, before the age of 12.
Section B is concerned with your experiences of travel and motion sickness **over the last 10 years**.
The correct way to answer each question is explained in the body of the questionnaire. It is important that you answer every question.
Thank you for your participation.

BACKGROUND QUESTIONS:

Name: _____

1. Please state your age. _____Years

2. Please state your Sex. Male [ ] Female [ ]

3. Please state you current occupation _____

4. Do you regard yourself as susceptible to motion sickness.

Not at all [ ] Slightly [ ] Moderately [ ] Very much so [ ]

SECTIONS A: Your childhood experience only (**before the age of 12**).

For each of the following types of transportation and entertainment please indicate with a √ :

5. As a child (before the age of 12) how often you **traveled or experienced**.

	Never	1 to 4 times	5 to 10 times	11 or more
Cars				
Buses (Greyhound, GO transit)				
Trains (VIA, GO transit)				
Aircraft				
Small boats Large boats (Ferries/ Ocean Liners)				
Swings				
Merry-go-rounds				
Amusement park rides				

6. As a child (before the age of 12) how often you **felt sick or nauseated**.

	Never	Rarely	Frequently	Always
Cars				
Buses (Greyhound, GO transit)				
Trains (VIA, GO transit)				
Aircraft				
Small boats Large boats (Ferries/ Ocean Liners)				
Swings				
Merry-go-rounds				
Amusement park rides				

7. As a child (before the age of 12) how often you **vomited**.

	Never	Rarely	Frequently	Always
Cars				
Buses (Greyhound, GO transit)				
Trains (VIA, GO transit)				
Aircraft				
Small boats Large boats (Ferries/ Ocean Liners)				
Swings				
Merry-go-rounds				

Amusement park rides				

SECTIONS B: Your experience over **the last 10 years** (approximately).

For each of the following types of transportation and entertainment please indicate with a √:

8. Over the last 10 years, how often you **traveled or experienced**.

	Never	1 to 4 times	5 to 10 times	11 or more
Cars				
Buses (Greyhound, GO transit)				
Trains (VIA, GO transit)				
Aircraft				
Small boats Large boats (Ferries/ Ocean Liners)				
Swings				
Merry-go-rounds				
Amusement park rides				

9. Over the last 10 years, how often you **felt sick or nauseated**.

	Never	Rarely	Frequently	Always
Cars				
Buses (Greyhound, GO transit)				
Trains (VIA, GO transit)				
Aircraft				
Small boats Large boats (Ferries/ Ocean Liners)				
Swings				
Merry-go-rounds				
Amusement park rides				

10. Over the last 10 years, how often you **vomited**.

	Never	Rarely	Frequently	Always
Cars				
Buses (Greyhound, GO transit)				
Trains (VIA, GO transit)				
Aircraft				
Small boats Large boats (Ferries/ Ocean Liners)				

Swings				
Merry-go-rounds				
Amusement park rides				

Thank you for your cooperation.

Reference: Golding, JF. 1998. Motion sickness susceptibility questionnaire revised and its relationship to other forms of sickness. Brain Research Bulletin 47(5):507-16.

Appendix F Rectal Probe Insertion Instructions and Technical Information

1. Clean your hands with the hand sanitizer provided.
2. Obtain the probe assembly in a sealed bag with an alcohol swab and packet of lubricant.
3. Clean the probe with the alcohol swab provided and let the probe dry.
4. Put a small amount of lubricant on the tip of the probe that will be inserted.
5. Lift one leg and slowly insert the probe to the small piece of tape that has been wrapped around the probe at the 15cm mark.
6. Tie the horizontal part of the T bandage around your waist at the front.
7. Bring the vertical part of the T bandage from the waist centre at the back, between the legs and tie it to the part of the bandage that is already around the waist. Make sure it is snug and will not slip down your body.
8. Put on your undergarments and clothing. Make sure you direct the connector end of the probe out the front waistband of your shorts, so it is accessible.
9. Clean your hands with the hand sanitizer provided.

Technical Information:

The Phillips Esophageal/Rectal Temperature Probe with 400 series Thermistor (Phillips Medical Systems Canada, Markham On) consists of an electrically insulated thermistor

permanently secured within a PVC tube. The thermistor is accurate within ± 0.1 ˚C from 25˚C to 45˚C.