

IMPACT OF “GO PILLS” ON FATIGUE, CIRCADIAN DESYNCHRONOSIS, ACCELERATION TOLERANCE AND PILOT PERFORMANCE



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Brooks City-Base Centrifuge





Purpose of Study



- **Assess impact of fatigue + circadian desynchronosis on**
 - **Flight performance parameters**
 - **+Gz tolerance & endurance**
- **Assess the impact of four stimulant drugs on**
 - **Flight performance during circadian nadir**
 - **+Gz tolerance**
 - **Subjective fatigue**
- **Explore the utility of a desktop flight simulator performance test battery**



Sustained Military Flying Operations-- Nothing New





Study Design



- **10 subjects (8 completed to date)**
- **Subjects tested after 19 hours of sustained wakefulness**
- **Testing during physiological circadian nadir (2-5 a.m. local time)**
- **Individual subject performance compared across conditions**
- **Drugs administered so that peak serum levels occurred during the circadian nadir**
- **Performance while using stimulants compared to night placebo and daytime baseline**



Simulated Mission Schedule



07:00-16:00	16:00	16:30	17:00	17:30	18:00	18:30	19:00	19:30	20:00	20:30	21:00	21:30	22:00	22:30	23:00
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Duty Day	FORM COMPLETION/movie/light snacks	Dinner	Pulse/BP	ANAM & F-PASS Testing	PVT	Snack	Ad lib	ANAM & F-PASS Testing
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23:30	0:00	0:30	1:00	1:30	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	4:30
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1st dose		2nd dose	PVT	ANAM	FPASS	Q	FUGE	Questionnaire			
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The Drugs



- **Dextroamphetamine** – Releases norepinephrine and dopamine resulting in direct stimulation of serotonin receptors leads to peripheral alpha and beta adrenergic stimulation
- **Methylphenidate (Ritalin ®)** – Dopaminergic CNS stimulant thought to work at RAS level, short-acting & results in less CNS dopamine depletion than dextroamphetamine
- **Pemoline (Cylert ®)** – Dopamimetic agent free of sympathomimetic activity; slow onset of action
- **Modafinil (Provigil ®)** – Stimulates alpha-2 and beta-adrenergic receptors—causes less less sympathetic stimulation, and possibly less interference with sleep



Study Hypothesis



- **Drugs with greater sympathomimetic effect should improve +Gz tolerance and endurance compared to night placebo:**

Dextroamphetamine, 10 mg >

Methylphenidate (Ritalin ®), 10 mg >

Modafinil (Provigil ®), 200 mg ≥

Pemoline (Cylert ®), 37.5 mg



CAUTION!



Results are Preliminary



Centrifuge Evaluation



- **30° tilt back F-16 seat without G suit**
- **+Gz tolerance assessment**
 - **Gradual onset run**
 - **Sequential rapid onset runs, without straining maneuver**
 - **Sequential rapid onset runs with strain**
- **+Gz endurance/tracking accuracy**
 - **Closed loop, simulated tactical aerial combat maneuver to 7 +Gz for maximum of 600 seconds**

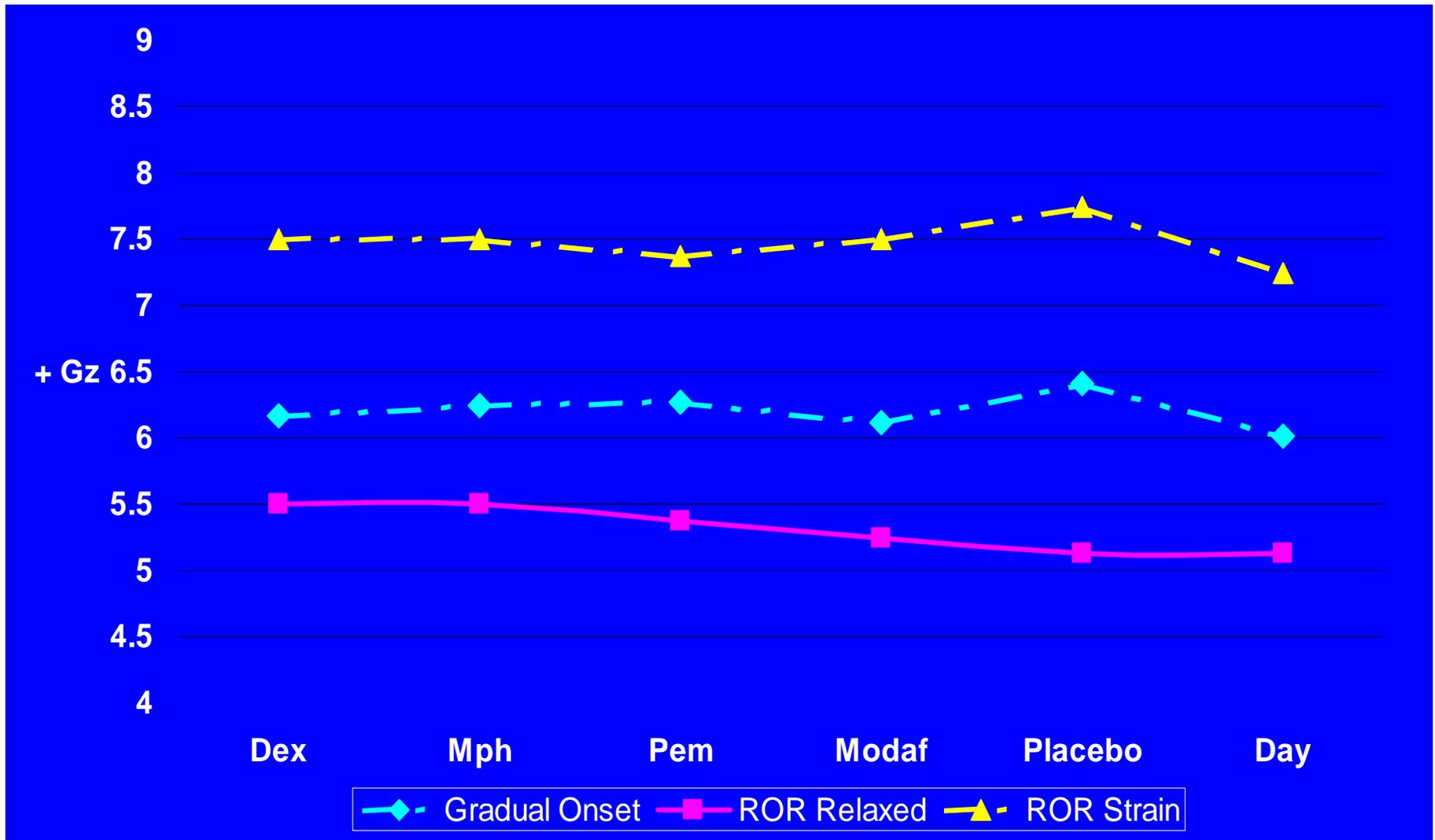


F-PASS Centrifuge Tracking Task



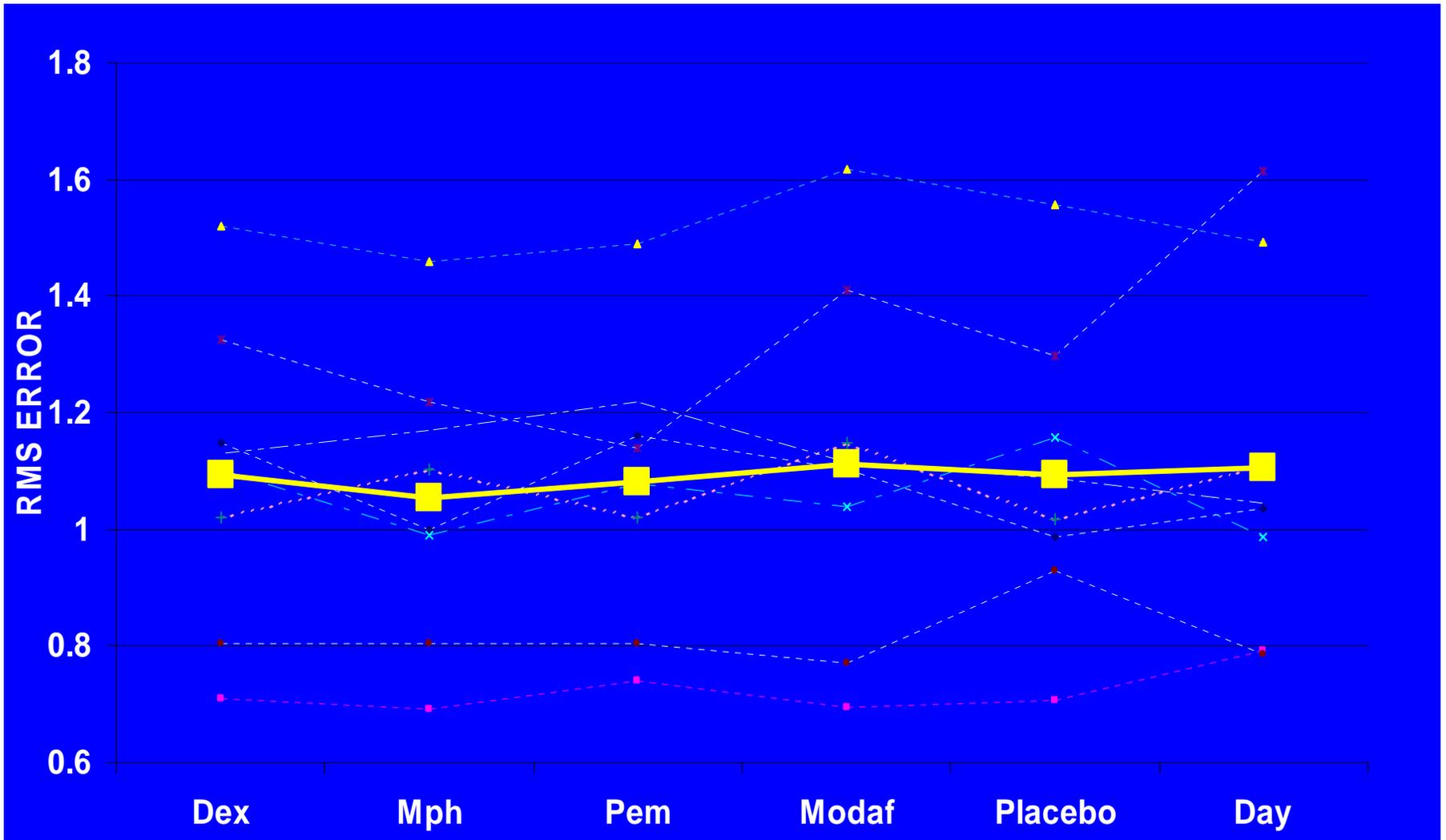


+Gz Tolerance Across Conditions



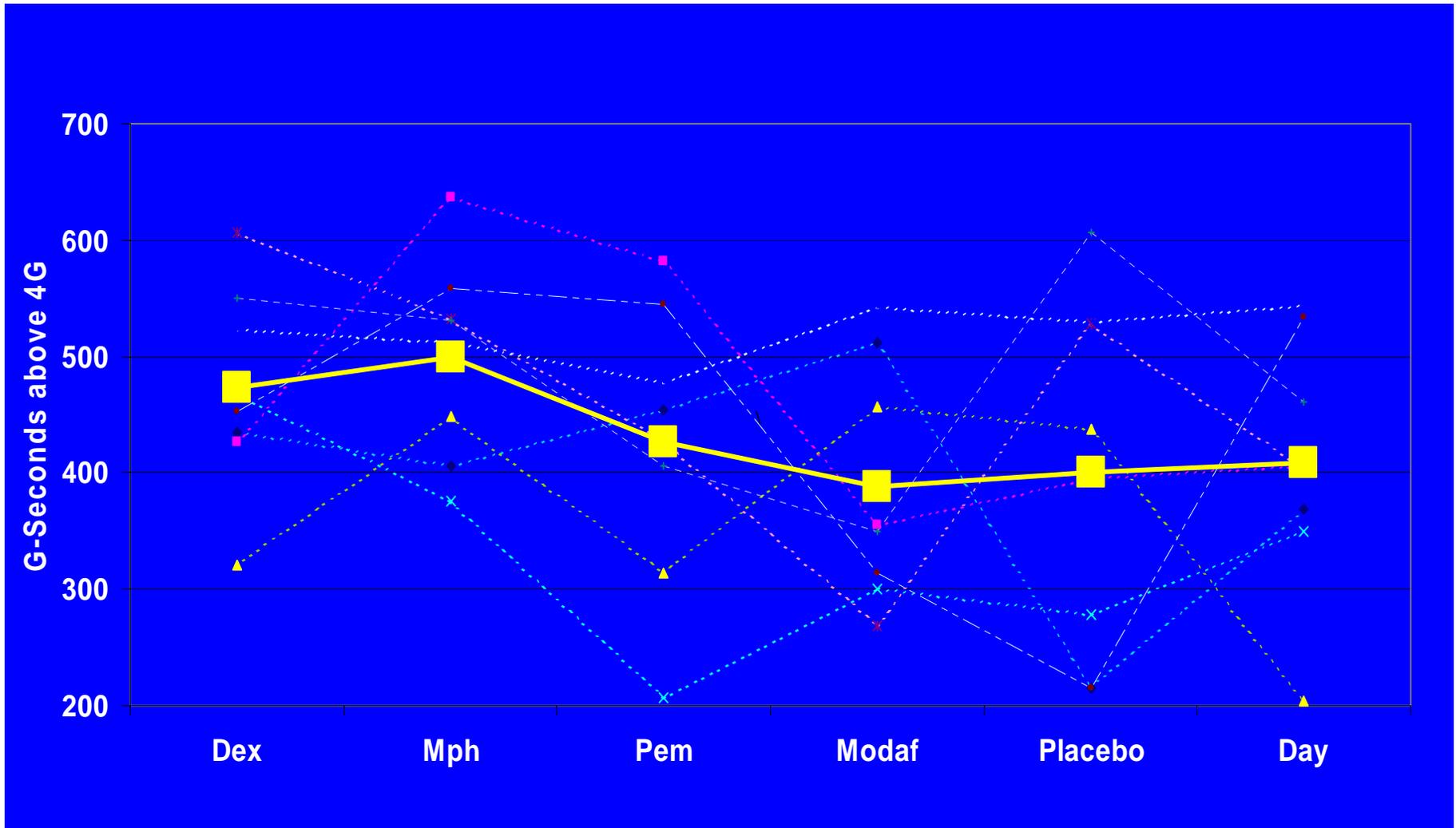


Centrifuge Target Tracking Accuracy



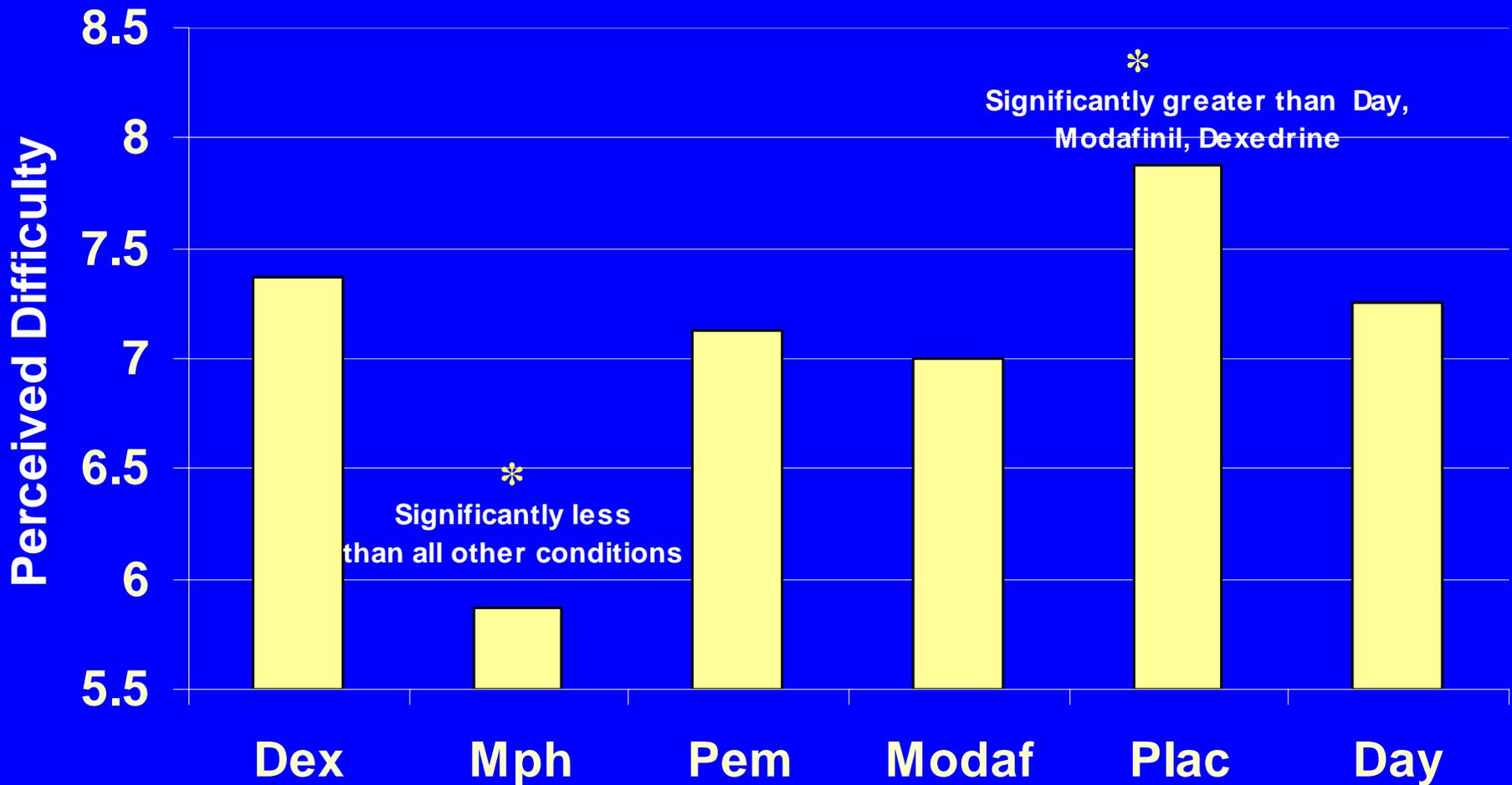


+Gz Endurance





Straining Difficulty



* P value < .05



Performance Parameters Measured



- **Automated Neuropsychological Assessment Metric (ANAM)**
 - Reaction time
 - Memory (short term/long term)
 - Mathematical reasoning/calculation
 - Eye/hand coordination
 - Visual vigilance
 - Spatial orientation
 - Ability to manage multiple simultaneous tasks
 - Mood
- **Subjective Assessment of Side Effects (via questionnaires)**
- **1 G (desktop) Flight Performance Assessment Simulation System (FPASS) (analysis pending)**
- **Simple Reaction Time (analysis pending)**



Performance Parameter Assessment



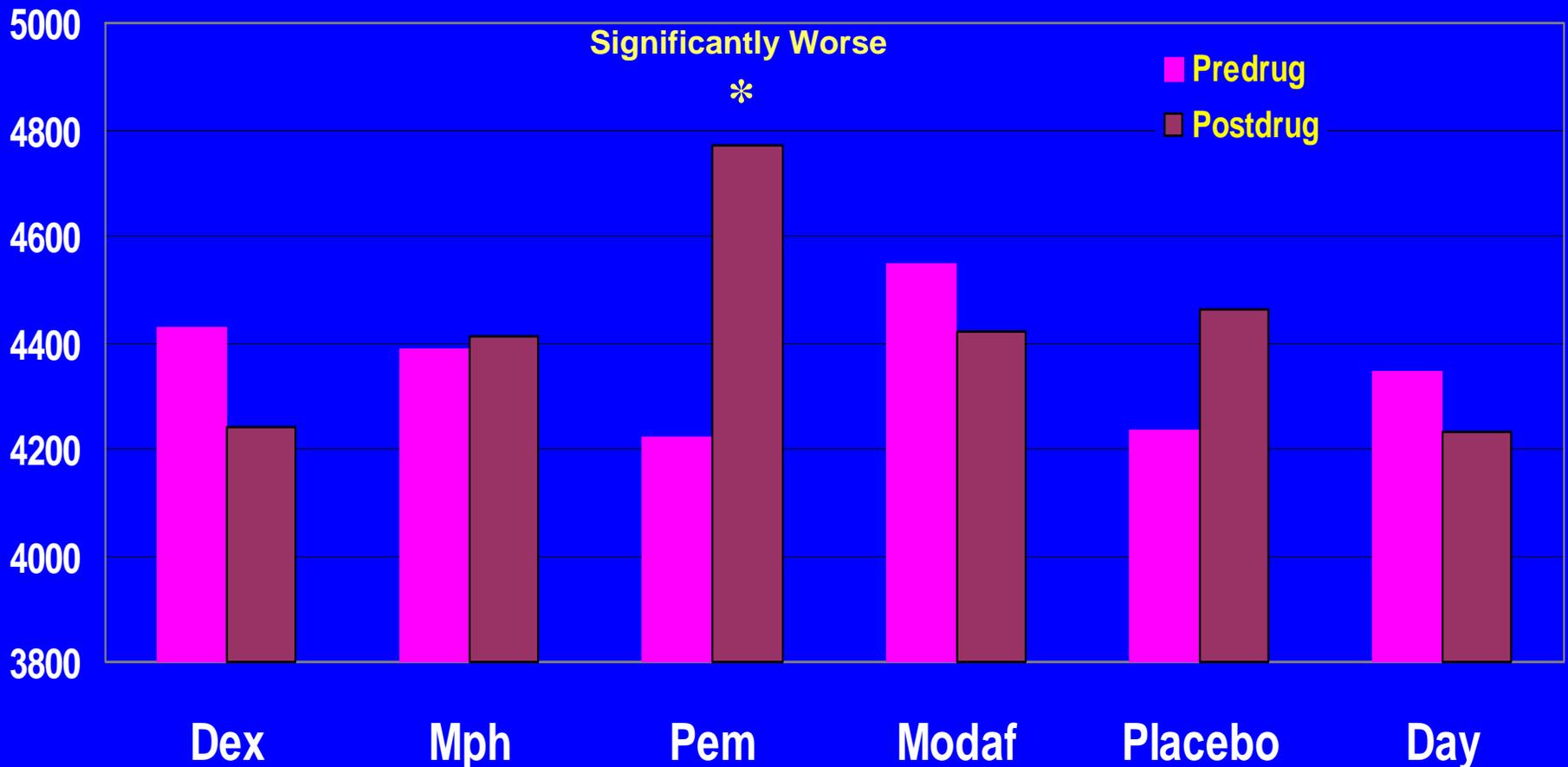
- **Testing at 10 p.m. before drug administration compared with tests administered between 2 and 5 a.m.**
- **Testing results compared against daytime baseline and night placebo**
- **Drug effects recorded during circadian nadir compared with daytime baseline and night placebo**



Grammatical Reasoning Mean Response Time



Mean Time Required for Abstract Analysis & Correct Response



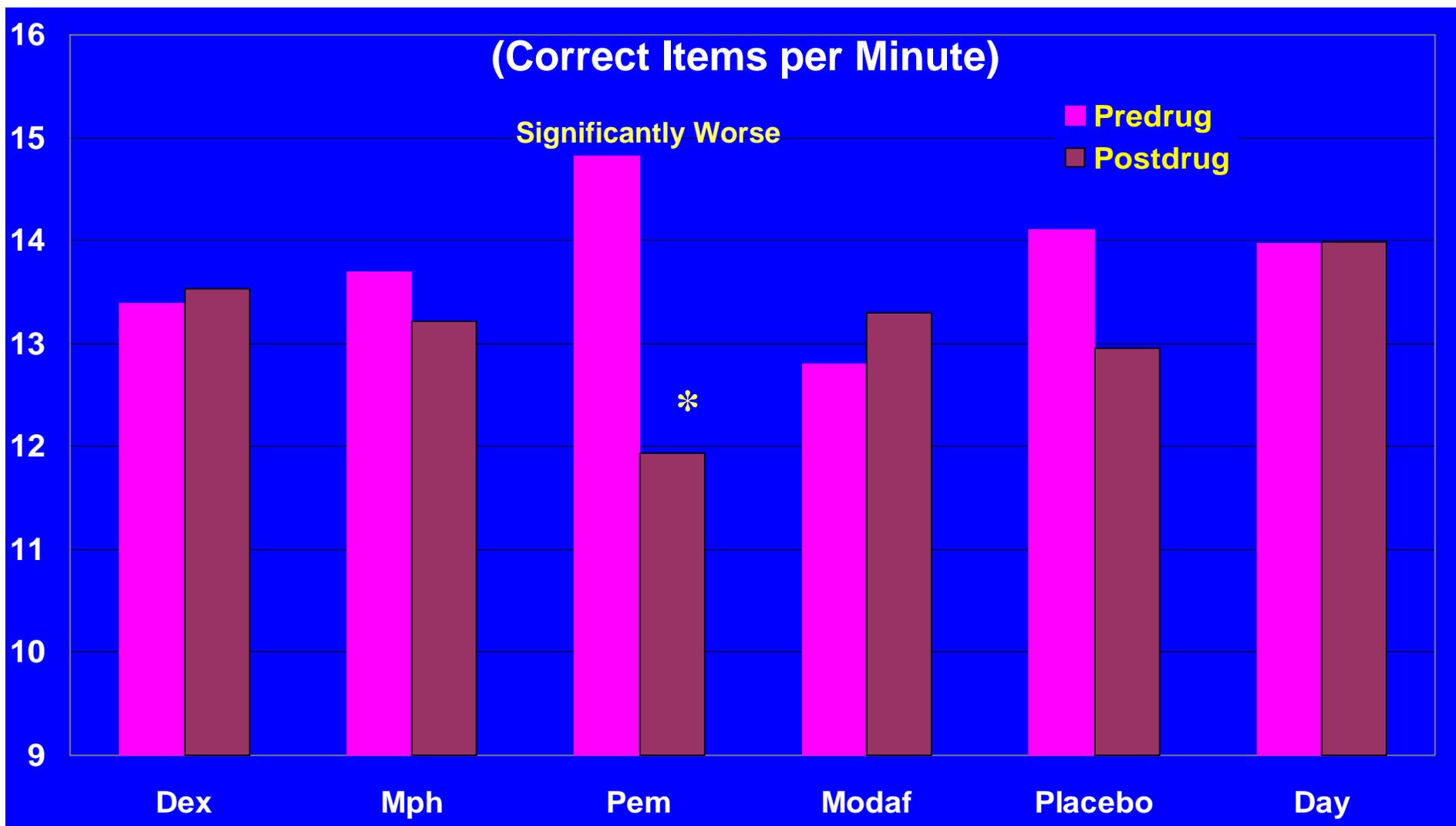
* P value < .05



Grammatical Reasoning Throughput



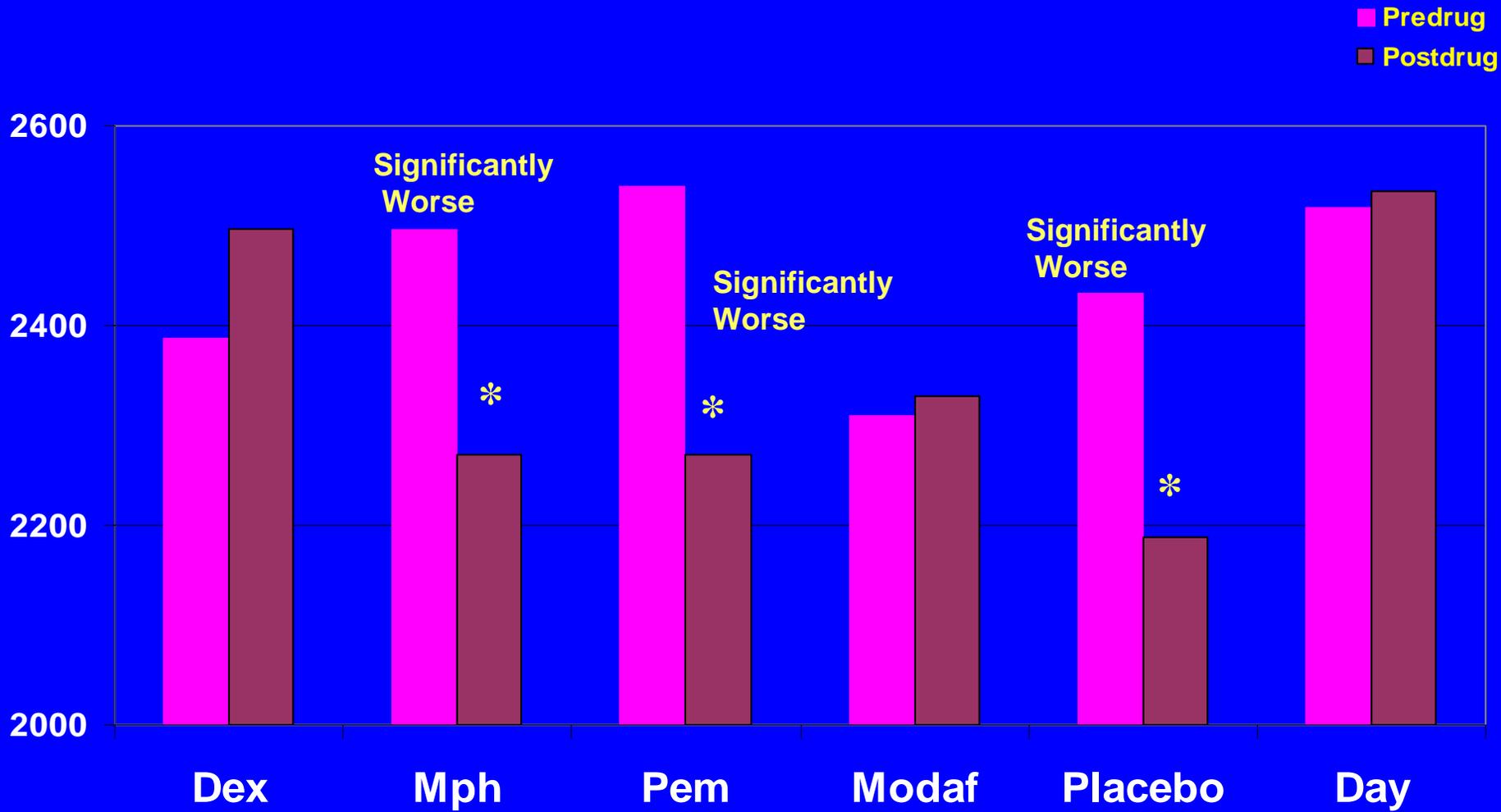
The Efficiency with which an Abstract problem was Analyzed



* P value < .05



Syn Win Complex Data Processing (Multitasking Composite Score)



* P value < .05



Reported Drug Effects



<i>Effect</i>	<i>Significant ($p \leq .05$)</i>	<i>Borderline Significant ($p = .051-.10$)</i>
Difficulty Staying Awake	Night Placebo > Day Baseline Night Placebo > Methylphenidate	
Sleepy	Night Placebo > Day Baseline, Dexedrine Methylphenidate > Day Baseline	Night Placebo > Day Baseline Dexedrine Pemoline Night Placebo > Pemoline
Ready to Fall Asleep	Night Placebo > Methylphenidate	Night Placebo > Dexedrine Pemoline
Difficulty Concentrating		Night Placebo > Day Baseline Modafinil Pemoline
Loss of Balance		Night Placebo > Dexedrine
Energetic	Day Baseline > All Conditions	Pemoline > Night Placebo
Alertness	Day Baseline > Placebo, Dex, Modaf, Mph	



Effects Not Reported, or Not Statistically Significant



- Restlessness
- Irritability
- Anxiety
- Confusion
- Euphoria
- Nervousness
- Apathetic
- Difficulty remembering
- Hallucinations
- Bad mood
- Tremor
- Lightheadedness
- Headache
- Faintness
- Chest pain
- Muscle in-coordination



Preliminary Conclusions



- **No clear advantage offered by any drug improving +Gz tolerance/endurance after 19 hours of sustained wakefulness during circadian nadir**
- **Suggestion of improved +Gz endurance with methylphenidate (not statistically significant)**
- **Methylphenidate reduced the difficulty associated with performing the L-1 & lower body anti-Gz straining maneuvers**
- **Dexedrine and modafinil sustained accuracy and speed in grammatical reasoning tests through the circadian nadir**
- **Dexedrine protected against fatigue/circadian nadir decrements in complex-/multi-tasking**



Preliminary Conclusions

(continued)



- **Dexedrine and modafinil mildly improved subjective measures of fatigue**
- **Pemoline does not appear to be a promising performance-enhancing drug**
 - **No +Gz tolerance or endurance advantage**
 - **No improvement in ease of performing strain**
 - **Demonstrated significant performance decrements in two grammatical reasoning tests**
 - **Does not improve subjective fatigue**
 - **Troublesome side effects: difficulty concentrating, sluggishness**



Research Directions



- **Complete G-MED study**
 - Data runs on last 2 subjects
 - Complete review of all behavioral and performance data
- **Suggested Future Initiatives**
 - Research chronic fatigue or longer periods of sleep deprivation
 - Study methylphenidate in pharmacologically equivalent dose to that of “Go Pill” dose of dextroamphetamine



Questions?



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