P330

Use of the Psychomotor Vigilance Test in clinical trials of CNS-active drugs: a systematic review and meta-analysis

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Introduction

- People with central disorders of hypersomnolence experience a range of cognitive difficulties, encompassing the domains of attention, executive functioning, and memory, with sustained attention being the most impacted aspect.[1]
- The Psychomotor Vigilance Test (PVT) has been used widely to explore abnormalities in, and changes to, sleep-wake cycles in healthy adults and in adults with central nervous system (CNS) disorders. However, the design of these studies and the PVT outcomes selected have varied widely.[2,3]
- Use of the PVT to measure sustained attention in placebo-controlled clinical trials of new drugs for sleep-wake disorders would be improved by knowledge of previous clinical trials, the therapeutic areas in which these occurred, the designs used, interventions studied, and the PVT outcomes selected.
- The design of new clinical trials using the PVT as an outcome would be facilitated by reference data that provide (1) ranges for normal performance, (2) examples of abnormal performance in known groups (ie, criterion validity), and (3) estimates of their sensitivity to change following sleep restriction or application of CNS-sedative drugs.

Objective

- To aggregate data from clinical trials in which the PVT has been used to determine the interventions and therapeutic areas studied, and the PVT outcomes used most. For the most common PVT outcomes, ranges for normal and abnormal performance and sensitivity to change were computed.

Methods

Study design

- A systematic review and meta-analysis were conducted of clinical trials of CNS-active compounds that included the PVT as an outcome (**Table 1**).

Analyses

- Each identified study was evaluated to determine:
  - The PVT outcomes used
  - The main study design and study population
  - The nature of the study sponsor
  - The drug studied.
- For the most commonly used PVT outcomes, data from previous studies were analyzed to provide estimates of normal ranges for performance, sensitivity to performance in groups with disorders that affect sleep-wake cycles (criterion validity), and sensitivity to change arising from sleep restriction or CNS-sedative drugs in healthy adults.

Table 1. PICOS criteria

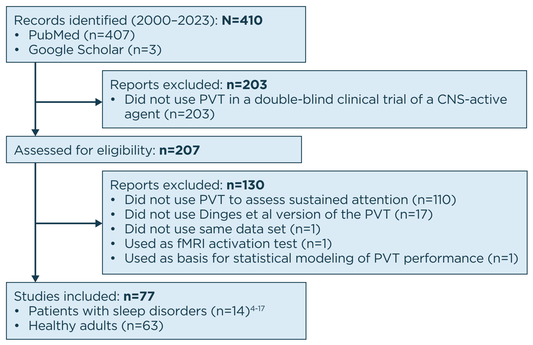
Population	Healthy adults and adults with diagnosed sleep disorders
Intervention	CNS-active compounds
Comparison	Placebo controlled
Outcomes	PVT outcomes
Study design	Randomized, placebo-controlled clinical trials conducted after 2000 Not a review, letter, meta-analysis, or opinion

Results

Study characteristics

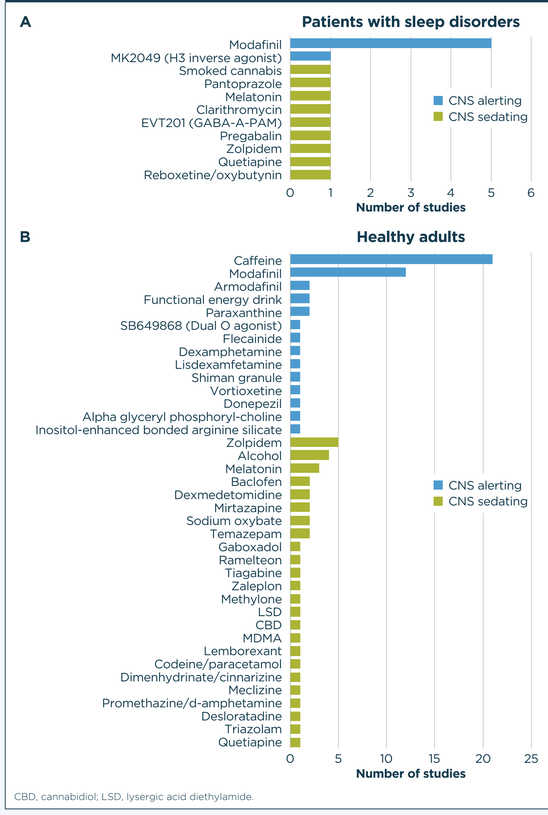
- Of 77 trials identified, 14 included patients with sleep disorders and 63 included healthy adults (**Figure 1**).
- For patients with sleep disorders, 65% of studies used a parallel-group design.
- For healthy adults, 68% used a crossover design, and for healthy adults with sleep disruption, 46% used a crossover design and 54% used a parallel-group design. In the healthy adults, 41 (53%) trials were conducted in the context of a sleep restriction challenge model (ie, experimenter-controlled disruption to normal sleep-wake cycles).
- 15 (19.5%) studies were sponsored by military organizations, 50 (64.9%) by academic institutions, 5 (6.5%) by pharmaceutical companies, 6 (7.8%) by academic institutions and pharmaceutical companies, and 1 (1.3%) by an academic institution and military organizations.
- CNS-alerting drugs were studied in clinical trials using PVT more often than CNS-sedating drugs; in healthy adults, CNS-alerting drugs were studied most often in the context of a sleep restriction challenge model (**Figure 2**).

Figure 1. Study inclusion



fMRI, functional magnetic resonance imaging.

Figure 2. Use of PVT outcomes in clinical trials



CBD, cannabidiol; LSD, lysergic acid diethylamide.

Outcome measures

- Among the 77 trials investigated, the PVT outcomes used most were the number of PVT lapses in attention, defined as reaction time (RT) >500 ms (57 [74.0%] trials) and speed of PVT performance, defined as the raw mean or median RT in ms (42 [54.5%] trials) (**Table 2**).

Table 2. PVT outcome measures used in clinical trials of CNS-active drugs

PVT outcome measure	N (%) of 77 studies identified in stage 1
N lapses	57 (74.0)
Raw mean or median RT	42 (54.5)
Reciprocal of raw mean/median RT	21 (27.3)
Fastest 10th percentile RT (raw or reciprocal)	19 (24.7)
Slowest 10th percentile RT (raw or reciprocal)	16 (20.8)
Total errors	6 (7.8)
Mean lapse duration	5 (6.5)
False starts	4 (5.2)
Log signal to noise ratio	3 (3.9)
SD of RT (raw or reciprocal)	3 (3.9)
Components of equations describing linear relationship between trial number and RT	2 (2.6)
Maximum RT (raw or reciprocal)	2 (2.6)
Hits	1 (1.3)

Reference framework for PVT outcomes

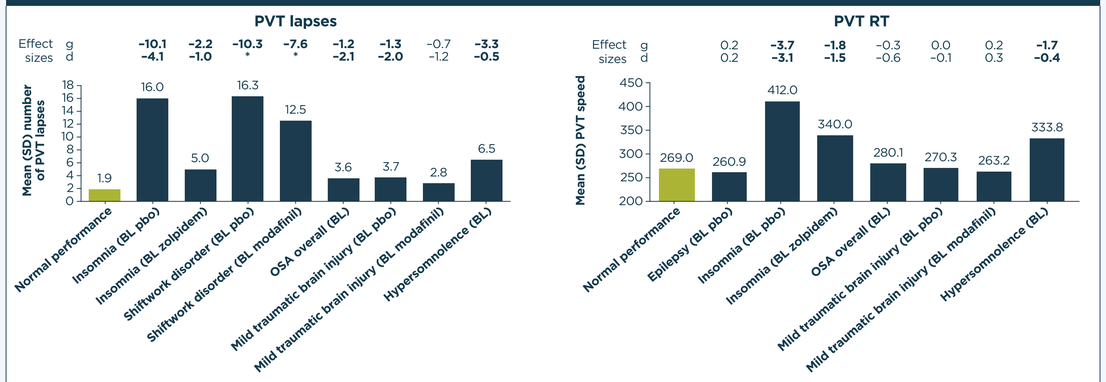
1. Ranges for normal performance

- Estimates for the normal range of performance for PVT number of lapses and PVT RT were estimated from baseline data for the 30 clinical trials that applied the PVT in healthy adults.
  - Healthy adults had an average of **1.88 (SD, 1.40) PVT lapses**, with an average **PVT RT of 269.01 (SD, 38.4) ms** (green bars in **Figure 3**).

2. Sensitivity to impairment

- Compared with PVT performance in healthy adults, adults with sleep disorders showed significant impairment on both PVT outcome measures (**Figure 3**).
  - Of the 2 performance measures, number of PVT lapses was more sensitive to the impairment in sustained attention that occurred in the patient groups.

Figure 3. PVT outcomes in patients with sleep disorders versus normal performance in healthy adults

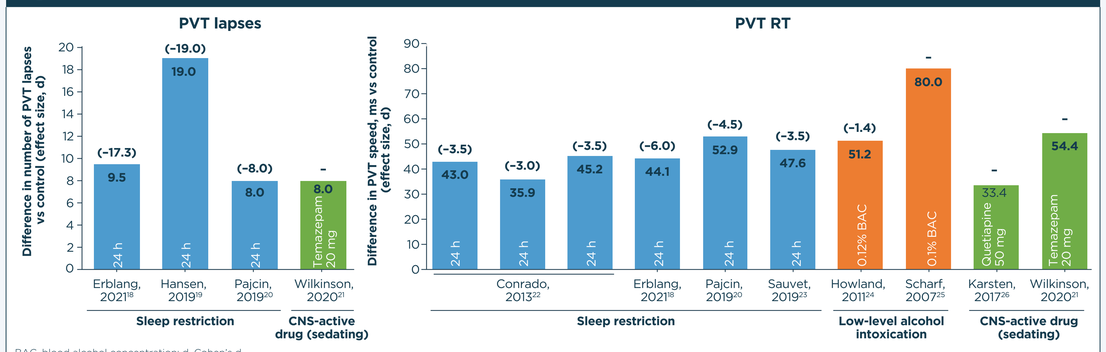


BL, estimated from pretreatment baseline; g, Hedges g; d, Cohen's d; OSA, obstructive sleep apnea; pbo, estimated from posttreatment placebo assessment.
Increased PVT lapses and PVT RT reflect greater impairment. Negative signs on effect sizes indicate that performance is worse than the control mean and vice versa. Bolded effect sizes are for differences that were ≥1 SD using the SD from the normative group (ie, Hedges g). *Indicates estimate of Cohen's d cannot be computed because of the absence of estimate of variance for the patient group.

3. Sensitivity to change in healthy adults

- The average decline in performance on 2 PVT endpoints, number of lapses, and PVT RT following 24 h of sleep restriction or treatment with a known CNS-sedative drug is summarized in **Figure 4**.
  - For PVT lapses, 24 h of sleep restriction was associated with increases of 8–19 lapses. Effect sizes for these declines were >2. Acute 20 mg temazepam was associated with a mean increase of 8 lapses.
  - For PVT RT, performance was also decreased substantially by 24 h of sleep restriction in healthy adults (~3 SD). PVT RT was decreased by a similar or greater magnitude following acute dosing with alcohol, quetiapine 50 mg, and temazepam 20 mg.

Figure 4. Effect of interventions on PVT outcome measures in healthy individuals



BAC, blood alcohol concentration; d, Cohen's d.
Increased PVT lapses and PVT RT reflect greater impairment. Negative signs on effect sizes indicate that performance is worse than the control mean and vice versa. Bold values indicate change scores that are equal to, or ≥1 SD, or for raw value on PVT speed was >38.4 msec or >3 lapses, defined as criteria for clinically meaningful change.

Conclusions

- **The PVT has been used widely in clinical trials to assess the effects of CNS-active compounds on sustained attention in healthy adults and in adults with sleep disorders.**
- **Performance on the PVT has been most commonly measured with the number of lapses or reaction time for correct responses.**
- **Compared with performance in healthy adults who have not undergone sleep restriction challenge, PVT lapses and reaction times are substantially impaired in adults with sleep-wake disorders.**
- **PVT lapses and reaction times become substantially worse following acute treatment with CNS-sedative drugs or by ≥24 h of sleep restriction in healthy adults.**
- **The common application of the PVT as an outcome in clinical trials shows that the main outcomes from this test are sensitive to both impairment and change in attentional processes.**
- **Together, these data provide a strong foundation for application of the PVT, and intepretation of performance data, in clinical trials that assess the ability of new CNS-active drugs to ameliorate impairment in sustained attention in sleep-wake disorders.**

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Acknowledgments: This work was funded by Takeda Development Center Americas, Inc. Under the direction of the authors, Christy Chao, PhD, and Lindsay Napier, PhD, CMPP, employees of Excel Scientific Solutions, Inc., provided writing assistance for this poster. Editorial assistance in formatting, proofreading, and copy editing was also provided by Excel Scientific Solutions, Inc. Takeda Development Center Americas, Inc., provided funding to Excel Scientific Solutions, Inc., for support in writing and editing this poster.

Disclosures: Brian T. Harel is an employee of Takeda Development Center Americas, Inc., and stockholder of Takeda Pharmaceutical Company Limited. Paul Maruff is an employee of Cogstate, contracted by Takeda for this work. Kiran Maski has been a consultant for Alkermes, Avadel, Eisai, Harmony Biosciences, Jazz Pharmaceuticals, Takeda, and Zevra Therapeutics, and has received research funding from Harmony Biosciences and Jazz Pharmaceuticals. Gert Jan Lammers has received consulting fees, grants, and travel funds from Alkermes, Bioprojet, Jazz, Takeda, Daiichi Sankyo, and Eisai. Claudio Bassetti has nothing to disclose. Robert D. Latzman was an employee of Takeda Development Center Americas, Inc., at the time of the study.

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SLEEP 2025 | Seattle, WA, USA | June 8–11, 2025

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