

Methylphenidate and the risk of acute central nervous system oxygen toxicity: a rodent model and observational data in human divers

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Keywords

ADHD; Attention deficit hyperactivity disorder; Diving; Hyperbaric oxygen; Seizures

Abstract

(Gur I, Arieli Y, Matsliah Y. Methylphenidate and the risk of acute central nervous system oxygen toxicity: a rodent model and observational data in human divers. *Diving and Hyperbaric Medicine*. 2024 30 September;54(3):168–175. doi: [10.28920/dhm54.3.168-175](https://doi.org/10.28920/dhm54.3.168-175). PMID: [39288920](https://pubmed.ncbi.nlm.nih.gov/39288920/).)

Introduction: The effects of methylphenidate, a stimulant often prescribed for the treatment of attention-deficit/hyperactivity disorder (ADHD), on the development of central nervous system oxygen toxicity (COT) have not been experimentally evaluated.

Methods: The records of all pure-oxygen-rebreather divers evaluated at our institution from 1975–2022 were assessed. Cases of COT were defined as a new onset of tinnitus, tunnel vision, myoclonus, headache, nausea, loss of consciousness, or seizures resolving within 15 minutes from breathing normobaric air, and matched 4:1 with similar controls. Any medications issued to the diver in the preceding three months, including methylphenidate, were recorded. In the animal arm of this study, male mice were exposed to increasing doses of methylphenidate orally, with subsequent exposure to hyperbaric O₂ until clinically evident seizures were recorded.

Results: Seventy-five cases of COT were identified in divers, occurring at a median of 80 (range 2–240) minutes after dive initiation at a median depth of 5 m (2–13). Hypercarbia was documented in 11 (14.7%) cases. Prescription of methylphenidate in the preceding three months was not associated with increased risk (OR 0.72, 95% CI 0.16–3.32) of COT. In mice, increasing methylphenidate exposure dose was associated with significantly longer mean COT latency time being 877 s (95% CI 711–1,043) with doses of 0 mg·kg⁻¹; 1,312 s (95% CI 850–1,773) when given 0.75 mg·kg⁻¹; and 1,500 s (95% CI 988–2,012) with 5 mg·kg⁻¹ (F = 4.635, P = 0.014).

Conclusions: Observational human data did not demonstrate an association between methylphenidate and an increased risk of COT. Methylphenidate exposure in mice prolongs COT latency and may have protective effects against COT.

Introduction

First synthesised in 1944, methylphenidate has been at the heart of pharmacotherapeutic approaches in the treatment of attention deficit for the past half a century. Diagnosed in over 2% of the adult population in the industrialised world and over 7% of children, attention deficit disorders (ADD) are the most common neurobehavioral disorders. The quick rise in the diagnosis of attention-deficit/hyperactivity disorders (ADHD) throughout the western world during the past two decades has made methylphenidate among the ten most prescribed medications in young adults.¹ Limited data suggest the prevalence of both ADD and methylphenidate use to be significant in divers.^{2,3} The reuptake inhibition of dopamine (as well as norepinephrine and to a lesser extent, an agonist effect on the serotonin 5HT1A receptor) is the main central nervous system (CNS) effect of methylphenidate. Clinically, neurostimulator effects predominate when methylphenidate is administered in both

human and animal subjects. While generally considered safe in children and adults, even with coinciding epilepsy, these recommendations are based mainly on registry-based data.⁴ Some observational studies showed a signal towards increased risk of seizures early after the initiation of methylphenidate.^{5,6}

Correlated with cerebral size and complexity, mammals, and particularly humans, are at increased risk of CNS oxygen toxicity (COT). While specific presentations may vary, generalised seizures and loss of consciousness are the most feared complications. In view of the potential for fatal drowning after sudden incapacitation underwater, coupled with the yet to be fully understood effects of immersion on COT risk, the maximal inspired PO₂ exposure limits are usually set to 284–304 kPa (2.8–3 atmospheres absolute [atm abs]) in dry conditions,⁷ and 142–182 kPa (1.4–1.8 atm abs) while submerged.⁸ However, personal susceptibility to COT is highly variable. Circadian rhythm,

exertion, environmental conditions such as ambient temperature or darkness, CO_2 levels, and exposure to various substances like caffeine or phenylephrine are just some of the modifiable factors to have been shown to alter susceptibility to COT.⁹

The effects of methylphenidate on COT susceptibility have not been experimentally evaluated thus far. Currently considered safe, these guidelines are based solely on expert opinion.¹⁰ A paucity of observational information and no systematically evaluated analyses have been published on the potential effects of methylphenidate on COT.¹¹

We aimed to investigate the potential influence of methylphenidate exposure on COT in a rodent model, coupled with an observational analysis of a large cohort of professional oxygen and mixed gas divers.

Methods

The human study was approved by our Institutional Ethics Committee (approval #2280-2022). The requirement for consent was waived by the ethics committee due to the retrospective nature of this study. The animal use protocol prepared for this study was reviewed and approved by our AAALAC-accredited Institutional Animal Care and Use Committee (approval #03-3415).

HUMAN SUBJECTS AND CASE DEFINITION

The medical records of all pure- O_2 rebreather military divers evaluated by the Israeli Naval Medical Institute (INMI) from 1 January 1975 to 31 December 2022 were included. Medical evaluation conducted bi-annually, includes a full list of medications, past medical history, otolaryngological and ophthalmological exams, a full cardiological workup (including a resting electrocardiogram, examination by a board-certified cardiologist, and ergometry for all candidates over the age of 35), a chest X-ray once every five years, spirometry, urinalysis, and complete blood count. In addition, all incidents involving a mild to moderate suspicion of oxygen toxicity (the onset of at least one of the following symptoms: tinnitus, tunnel vision, myoclonus, new headache, or nausea) are mandatorily reported to INMI, with severe cases (involving loss of consciousness and/or seizures) actively investigated including a full forensic equipment evaluation by our specialised laboratory.

For the purposes of this study, to be defined as COT, any case must have: 1) occurred during a dive using a pure O_2 rebreather system; 2) manifested as a new onset of tinnitus, tunnel vision, myoclonus, headache, nausea, loss of consciousness or seizures only after the dive began; 3) resolved within 15 minutes when normobaric air was administered (in case of a seizure, this maximum recovery period referred to the tonic-clonic phase and excluded any postictal manifestations such as decreased consciousness or confusion); and 4) no other explanation (including

hypoxia from any cause or trauma) was found on an active investigation. Controls were matched at a 4:1 ratio with divers from similar recruitment years to allow for maximal matching of potential confounders like age, diving experience, and exposure profiles. Medication exposure was determined by reviewing dispensary records, which due to the centralised (single payer and single provider) nature of military healthcare, meticulously document any medication issued, including those considered 'over the counter'. Any prescription given over the previous three-month period was recorded as positive for drug exposure (e.g., methylphenidate, acetaminophen, etc.). During the study years, only immediate-release methylphenidate prescribed for the indication of ADHD was allowed. Other stimulants, as well as methylphenidate prescription for other indications (sleep disorders, off-label, etc.), were not permitted by military regulations in the study population.

ANIMALS AND PHARMACOTHERAPY

Mice were chosen as previous evidence suggests this species exhibits lower variability in COT latency when compared to other rodents, particularly rats.¹² Twenty male Institute of Cancer Research mice (mean 32.1 [SD 2.6] g, range 28–38 g), (Harlan Laboratories, Indianapolis, IN, USA) aged eight weeks were included in this study. Methylphenidate was given orally, after the following preparation: 1) Immediate-release methylphenidate was dissolved in 20 μL of sterile water to achieve a total administered dose of 0.75 $\text{mg}\cdot\text{kg}^{-1}$, previously demonstrated to correspond to human therapeutic doses, achieving the target plasma concentration of 6–10 $\text{ng}\cdot\text{mL}^{-1}$ within 15 minutes.¹³ 2) Another dose of 5 $\text{mg}\cdot\text{kg}^{-1}$ was chosen to investigate a potential dose effect. This higher concentration was chosen for being at the cusp of previously reported LD_{50} for mice⁶ and pharmacodynamic investigations in both rodent and human models.^{1,13} After examining different feeding methods, and striving to avoid gavage or the need for orogastric cannulation and the associated stress-related increase in the risk of COT,⁹ dissolving the administered dose in peanut butter following 16 hours of starvation was found to be the most effective method of drug administration. This approach was supported by previous evidence of unaltered pharmacokinetics of methylphenidate with regards to feeding status.¹² This also allowed for standardisation of caloric intake prior to hyperbaric oxygen exposure, since reduced caloric intake and starvation were linked with decreased risk of COT.⁷ Seizures were defined as the onset of regular tonic-clonic twitches (limbs, head, or tail). Any isolated myoclonia (limb twitch, tail hardening, etc.) were disregarded.

HYPERBARIC CHAMBER SETUP AND EXPOSURE PROFILES

Video surveillance was continuous throughout the hyperbaric exposure, as were chamber conditions including temperature, humidity and O_2 concentration (Servomex®, Crowsborough,

East Sussex, UK). Following the administration of dissolved immediate release methylphenidate or water (placebo) as described above, the mouse was placed in a well-ventilated cage, preventing heat and CO₂ accumulation as hypercarbia is a strong predictor of COT.⁷ Compression was initiated 90 minutes after the drug was administered, allowing for peak blood concentration to be reached. Compression to 506 kPa (5 atm abs) was achieved over 10 minutes, followed by the saturation of the hyperbaric chamber with 100% O₂. This hyperbaric oxygen exposure was continued until seizures were observed, at which point air was flushed through the chamber and the chamber was decompressed to normobaric pressure at 101.3 kPa (1 atm abs) per minute. Chamber temperature was maintained at 25–30°C.

Five mice served as controls throughout the experiment (exposure group A). Eight were exposed to a placebo followed by 0.75 mg·kg⁻¹ and then 5 mg·kg⁻¹ of methylphenidate (group B). Seven were exposed to a placebo, followed by 5 mg·kg⁻¹ and then 0.75 mg·kg⁻¹ of methylphenidate (group C). The study design is presented in Figure 1. Exposures were spaced seven days apart, allowing for potential effects of previous hyperbaric exposure and the resultant decrease in seizure latency to wear off.⁹

STATISTICAL ANALYSIS

Human case-control study

Standard descriptive statistics were used to summarise population characteristics. The low prevalence of methylphenidate exposure in the human (observational) portion of this study allowed for the odds ratio (OR) to serve

as a reasonable estimator of risk. Adjustment for possible interactions was achieved by constructing a multivariate logistic regression model using Pearl and Reed's method.¹⁴

Animal model

Fisher's least significant difference (LSD) correction was applied when applicable to adjust for multiple comparisons for the mice data. Analysis of variance was performed when comparing COT latency time after normal distribution was ascertained by means of QQ plot visual analysis as well as skewness and kurtosis $\leq |2|$. A repeated measures general linear model was constructed to allow for within-group comparison of the effects of varying methylphenidate exposure on the same animal. Levene's test for homoscedasticity and an unpaired *t*-test were performed on exposure groups B and C in matching drug doses. Groups B and C were pooled (by drug dose) only if Levene's test yielded nonsignificant ($P > 0.01$) results. A 2-sided $P < 0.05$ was considered statistically significant for all tests. All calculations were performed using SPSS software version 24.0.

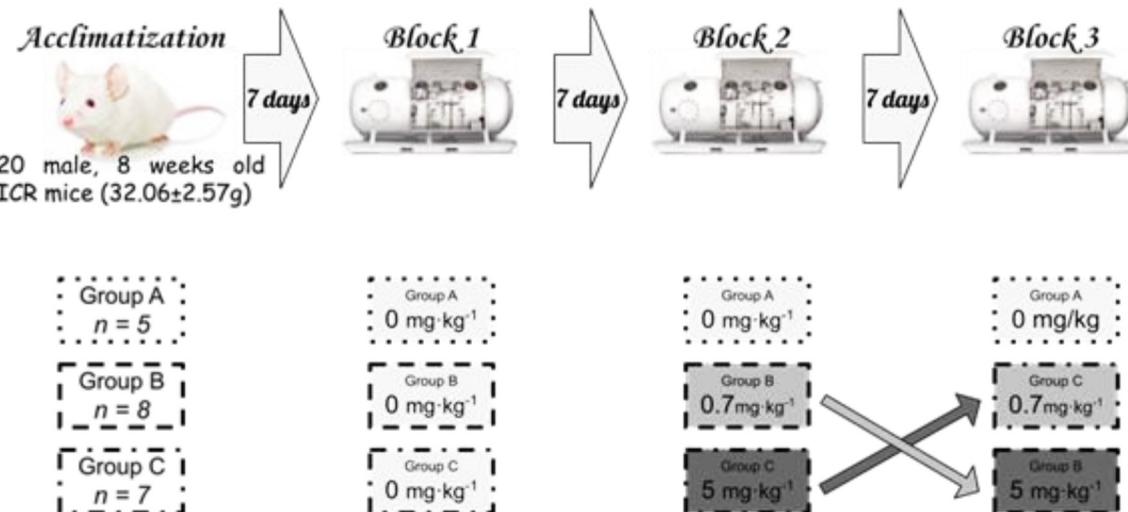
Results

HUMAN CASES AND CONTROLS

A total of 75 cases of COT in humans were identified as matching our case definition. The median latency time, defined as time from dive initiation to the appearance of symptoms, was 80 minutes (IQR 26–135) (range 2–240). The median bottom depth was 5 metres of sea water (IQR 4–6) and the median water temperature was 22°C

Figure 1

A schematic representation of the animal study protocol; in each block, mice were compressed to 506 kPa (5 atm abs) over 10 mins, followed by pure O₂ breathing until seizures were observed. All doses refer to methylphenidate administered orally. ICR – institute of cancer research



(IQR 18–25) (range 13–30). In 44 COT cases (58.7%) the diver was appropriately dressed as mandated by our diving physiology research laboratory guidelines.¹⁵ Hypercarbia (mainly attributed to scrubber dysfunction) was recorded in 11 cases (14.7%). Diving profiles involved a constant depth ('square') in 42 cases (56%), whereas 20 (26.7%) involved a gradual ascent ('repet-up') and 13 (17.3%) were not homogeneous ('hang-off' or 'yo-yo' dives). Exertion was maximal (estimated above 15 metabolic equivalents) in 25 (33%) cases, moderate (fin swimming) in 32 (42.7%), and

minimal (using a propulsion vehicle) in 18 (24%). These findings, along with a comparison to matched controls in baseline characteristics, are presented in Table 1 and Table 2.

Comparing cases of COT to controls, the OR for methylphenidate exposure at any dose during the antecedent three months (but not within 24 hours before diving) was 0.72 (95% CI 0.16–3.32). Adjusted for age, body mass index, diving experience, smoking, history of attention deficit disorder or allergic rhinitis, and recent (within three

Table 1

Baseline characteristics of central nervous system oxygen toxicity (COT) cases and matched controls; ¹ Any tobacco use within prior six months; ² History of mild vasomotor rhinitis or allergic rhinitis with no active disease or treatment during the past two years; ³ Attention deficit disorder, with or without hyperactivity, diagnosed by a certified psychiatrist/neurologist in accordance with DSM-V criteria, with no significant functional limitation or comorbidity, irrespective of the need for psychopharmacotherapy; ⁴ Asymptomatic mild impairments, such as kyphosis < 50 degrees, scoliosis < 20 degrees, over two years from simple uncomplicated fracture with no sequela, partial meniscectomy/meniscal tear with no sequelae or functional limitation and mild pes planus; ⁵ Refractive deficit of ± 1.75 diopter (spherical or astigmatism) or less, provided uncorrected visual acuity is 6/9 (20/30) or better; ⁶ Provided disease deemed inactive and serology negative for the past six months; ⁷ Varicocele or hydrocele provided no functional limitation is present (including surgery with no sequelae completed more than two years prior); ⁸ Any medications prescribed within the prior six months

Parameter	Cases <i>n</i> = 75	Controls <i>n</i> = 300	<i>P</i>
Age (years), Median (Range)	20 (18–27)	21 (18–27)	
18–21 years, <i>n</i> (%)	52 (69.3)	203 (67.7%)	0.782
22–25 years, <i>n</i> (%)	18 (24.0)	79 (26.3%)	0.680
> 25 years, <i>n</i> (%)	5 (6.7)	18 (6.0%)	0.830
Morphometrics, Mean (standard deviation)			
Height, cm	178.0 (5.3)	178.4 (5.8)	0.626
Weight, kg	75.4 (6.1)	76.6 (7.9)	0.198
Body mass index, kg·m ⁻²	23.8 (1.3)	24.1 (1.9)	0.210
Total pure O₂ diving experience, <i>n</i> (%)			
< 100 hours	25 (33.3)	91 (30.3)	0.615
100–500 hours	30 (40.0)	103 (34.3)	0.359
> 500 hours	20 (26.7)	106 (35.3)	0.155
Background diagnoses, <i>n</i> (%)			
Smoking ¹	5 (6.7)	23 (7.7)	0.768
Allergic rhinitis/sinusitis ²	2 (2.7)	3 (1.0)	0.260
Attention deficit ³	7 (9.3)	36 (12.0)	0.517
Significant orthopedic history ⁴	9 (12.0)	42 (14.0)	0.651
Refractive error/correction ⁵	3 (4.0)	5 (1.7)	0.211
Celiac ⁶	2 (2.7)	4 (1.3)	0.410
Varicocele ⁷	3 (4.0)	7 (2.3)	0.423
Medications previously prescribed⁸, <i>n</i> (%)			
Methylphenidate	2 (2.7)	11 (3.7)	0.672
Decongestants	7 (9.3)	22 (7.3)	0.562
Antihistamine	9 (12.0)	34 (11.3)	0.871
NSAIDs	22 (29.3)	95 (31.7)	0.696
Acetaminophen	46 (61.3)	178 (59.3)	0.752

Table 2

Central nervous system oxygen toxicity (COT) dive characteristics;
¹ Estimated METs > 15;² see (Ofir et al. 2019)¹⁵;³ Any indication of potential hypercarbia or CO₂ scrubbing dysfunction, including deficient soda lime, damaged scrubber container or any damaged one-way valves

Parameter	n (%)
Time of day	
05:00–22:59	32 (42.7)
23:00–04:59	43 (57.3)
COT latency, minutes	
< 60	28 (37.3)
60–119	21 (28.0)
120–179	15 (20.0)
≥ 180	11 (14.7)
Exertion	
Diver propulsion vehicle	18 (24.0)
Swimming	32 (42.7)
Maximal exertion ¹	25 (33.3)
Diving profile	
Square	42 (56.0)
Repet-up	20 (26.7)
Hang-off	13 (17.3)
Maximal depth, metres	
< 4	15(20.0)
4–6	43(57.3)
> 6	17(22.7)
Water temperature, °C	
< 19	22 (29.3)
19–23	22 (29.3)
> 23	31 (41.3)
Appropriate garment ²	44 (58.7)
Other	
Hypercarbia ³	11(14.7)

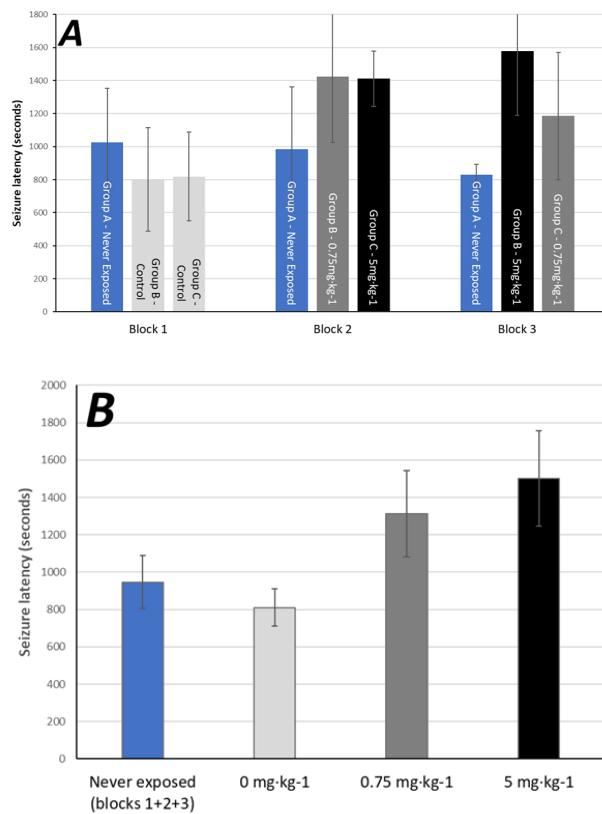
months) use of decongestants, antihistamines or analgesics the adjusted OR for methylphenidate exposure was 0.87 (95% CI 0.14–5.29), as presented in * [Supplementary Table 1](#). Reviewing individual cases, no medications were used in the 24 hours preceding the COT event.

RODENT MODEL

Increasing methylphenidate exposure in mice was associated with significantly longer COT latency time ($F = 4.635$,

Figure 2

A. Seizure latency with varying methylphenidate exposure; mean central nervous system oxygen toxicity (COT) latency time (from reaching chamber pressure of 506 kPa [5 atm abs] to the occurrence of tonic-clonic twitches) is presented by study group and block. B. Latencies are grouped by methylphenidate dose and also compared to mice never exposed to methylphenidate (study group A). Error bars represent 95% confidence intervals. The difference between average latency times for the 5 mg·kg⁻¹ group compared with those of the 0 mg·kg⁻¹ (control) group reached statistical significance ($P = 0.015$)



$P = 0.014$). Pooling COT latency times by methylphenidate exposure dose showed a mean latency of 1,500 s (95% CI 988–2,012) when mice were given 5 mg·kg⁻¹, 1,312 s (95% CI 850–1,773) for 0.75 mg·kg⁻¹, 809 s (95% CI 607–1,010) for 0 mg·kg⁻¹ (treatment group B and C) and 946 s (95% CI 660–1231) for controls (treatment group A). These are presented in Figure 2.

Post-hoc analysis indicated latency time to be significantly longer comparing the 5 mg·kg⁻¹ dose to controls (877 s vs 1,500 s, LSD corrected Md 622 s [95% CI 183–1,061], $P = 0.006$), while comparing 0.75 mg·kg⁻¹ to controls approached statistical significance (1,312 s vs 1,500 s, LSD corrected Md 434 s [95% CI -93–961], $P = 0.052$). These findings were unchanged when adjusted to animal weight and chamber temperature by constructing a general linear

* Footnote: [Supplementary Table 1](#) is available on the DHM Journal website.

Table 3

Hyperbaric oxygen-induced central nervous system oxygen toxicity (COT) seizure latency (seconds) in mice; Analysis of variance (ANOVA) was performed to investigate potential variability in average COT latency times between the different exposure groups, both when all cases were included and when only looking at the subset of mice treated with different doses of methylphenidate (groups B and C). A general linear model accounting for animal weight and chamber temperature is presented in the bottom portion. The righthand portion depicts post hoc analyses (corrected for multiple comparisons) investigating the difference in COT latency times between specific exposure groups, both overall and in the exposed animals (groups B and C). CI – confidence interval; MD – mean difference

Overall		Post hoc (corrected by Fisher's least significant difference)									
		0.75 vs 0 mg·kg ⁻¹			5 vs 0 mg·kg ⁻¹			5 vs 0.75 mg·kg ⁻¹			
F	P	MD	95% CI	P	MD	95% CI	P	MD	95% CI	P	
Analysis of variance, all cases included											
4.635	0.014	434.3	-4.78–873.38	0.052	622.83	183.75–1,061.92	0.006	188.53	318.48–695.54	0.460	
Only treatment groups B and C (repeated measure analysis of variance)											
3.416	0.042	502.6	-49.07–1,054.27	0.073	691.13	139.46–1,242.81	0.015	188.53	363.14–740.21	0.494	
General linear model adjusted for weight and chamber temperature											
4.308	0.018										

model ($F = 4.308$, $P = 0.018$). A repeated measure analysis of variance including only mice exposed to methylphenidate (treatment groups B and C) showed similar trends ($F = 3.416$; $P = 0.042$; post-hoc $5 \text{ mg} \cdot \text{kg}^{-1}$ vs control MD 691s, [95%CI 139–1,242], $P = 0.015$). Analysing mice unexposed to methylphenidate (treatment group A) showed no significant difference in COT latency ($F = 0.756$, $P = 0.542$). All measurements are presented in Table 3.

Discussion

Our analysis found no increased risk of COT to be associated with chronic methylphenidate exposure (with no documented use of the drug in the 24 hours before diving) in humans, albeit the low prevalence of methylphenidate exposure underpowered our ability to detect minor increases in risk. Moreover, since no divers reported taking any medications in the vicinity of documented COT events, our human data cannot shed light as to the short-term safety of methylphenidate use with regard to COT risk. Considering the likely underreporting in the highly motivated group of military divers, we deem the immediate exposure data (beyond pharmacy records) to be of low reliability. Finally, the low incidence of COT in human divers limits our ability to truly estimate the potential effect of methylphenidate withdrawal on the risk of COT.

The rodent model, undertaken in an attempt to bridge this knowledge gap, seems to establish a certain protective property of methylphenidate on the risk of COT. Our data suggests an association between methylphenidate dose and increasing COT latency.

Increased sympathomimetic activity may increase the risk of COT, as evident from the association between strenuous exercise, stress, circadian rhythm disturbance and hypothermia.⁷ This notion is consistent with our findings

of the epidemiological characteristics of documented COT events. Sympathomimetic agents, such as pseudoephedrine, were also shown in rodent models to increase the risk of COT.⁹ The weak increase in CNS norepinephrine as a result of methylphenidate administration¹⁶ is therefore an unlikely explanation for such COT protective effects.

We believe the mechanism may be related to increasing levels of dopamine. Methylphenidate was repeatedly shown to significantly increase dopamine levels in various brain regions in different rodent and primate models.^{4,6,13,16} Striatal dopamine levels were previously shown to decrease under increasing partial pressures of oxygen, with critically low levels resulting in COT-induced seizures in rats.^{17,18} Caffeine, a substance shown to increase striatal dopamine receptor availability, has been demonstrated to delay convulsions in rats.¹⁹ Methylphenidate's dopaminergic effects thus may help explain its neuroprotective properties in delaying critical COT-inducing low levels of dopamine. Such a mechanism would not apply to prolonged use of other stimulants, e.g., methamphetamines, shown to cause degeneration of dopaminergic terminals in the striatum,²⁰ which might increase the risk of COT.

Of note, dopamine hypoactivity has been suggested as a potential pathophysiological pathway at the core of ADHD. For instance, expression of the dopamine transporter was shown (using single photon emission tomography) to be 70% higher in the striatum of patients with ADHD compared with controls.²¹ Such a deficit may increase inappropriate connectivity to the prefrontal cortex. Treatment with methylphenidate has been shown to decrease the dopamine transporter density.²² In other words, divers with ADHD who are currently not treated with methylphenidate (e.g., did not take this medicine in the hours leading to the dive) may thus have dopaminergic hypoactivity, previously shown to increase COT susceptibility.⁷ Our data do not

suggest an increased risk of COT in patients with ADHD who are prescribed methylphenidate, all of whom stop the medication at least 24 hours before the dive. However, we are underpowered and methodologically ill equipped to answer this interesting question – namely, are patients on methylphenidate at increased risk of COT if they dive without this medication.

LIMITATIONS

This study has several important limitations. The relative rarity of COT confounded us to the case-control design in human subjects and only to pure O₂ rebreather divers. Since these systems are used almost exclusively by elite, very young, highly trained, and overwhelmingly male divers, the generalisability of our findings to other populations of mixed-gas divers or HBO patients is limited. The animal arm of this study is limited by the great differences between our rodent model and cerebral complexity in humans, easily evident by the immensely higher PO₂ needed to induce COT in our model animals. Importantly, we were unable to investigate the effects of immersion in our model animals. This is important since immersion is consistently shown to increase COT susceptibility, practically halving the COT threshold in humans.⁷

Conclusions

Observational human data suggests methylphenidate is not associated with an increased risk of COT. Methylphenidate exposure in mice increases COT latency, and may have protective effects against COT.

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Conflicts of interest and funding

This study was funded by the Israel Ministry of Defense – Directorate of Defense Research and Development (IMOD DDR&D). No conflicts of interest were declared.

Submitted: 5 February 2024

Accepted after revision: 7 June 2024

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