

Review article

Systematic review on the effects of medication under hyperbaric conditions: consequences for the diver

Erik Hoencamp¹, Thijs TCF van Dongen^{2,3}, Pieter-Jan AM van Ooij⁴, Thijs T Wingelaar⁴, Mees L Vervelde⁵, Dave AA Koch⁴, Rob A van Hulst^{4,6}, Rigo Hoencamp^{2,3,7}

¹ *Institute of Psychology, Leiden University, Leiden, The Netherlands*

² *Defense Healthcare Organization, Ministry of Defense, Utrecht, The Netherlands*

³ *Department of Surgery, Alrijne Hospital, Leiderdorp, The Netherlands*

⁴ *Diving Medical Center, Royal Netherlands Navy, Den Helder, The Netherlands*

⁵ *Central Military Hospital, Ministry of Defense, Utrecht*

⁶ *Department of Anesthesiology, Academic Medical Center, Amsterdam, The Netherlands*

⁷ *Division of Surgery, Leiden University Medical Center, Leiden*

Corresponding author: Thijs TCF van Dongen, Department of Surgery, Alrijne Hospital, PO Box 4220, 2350 CC Leiderdorp, Simon Smitweg 1, 2353 GA Leiderdorp, The Netherlands

tcfvandongen@alrijne.nl

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Abstract

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Background: Physiological changes are induced by immersion, swimming and using diving equipment. Divers must be fit to dive. Using medication may impact the capacity to adapt to hyperbaric conditions. The aim of this systematic review is to assess the interaction of diving/hyperbaric conditions and medication and to provide basic heuristics to support decision making regarding fitness to dive in medicated divers.

Methods: This was a systematic review of human and animal studies of medications in the hyperbaric environment. Studies were subdivided into those describing a medication/hyperbaric environment interaction and those concerned with prevention of diving disorders. Studies without a relation to diving with compressed air, and those concerning oxygen toxicity, hyperbaric oxygen therapy or the treatment of decompression sickness were excluded.

Results: Forty-four studies matched the inclusion criteria. Animal studies revealed that diazepam and valproate gave limited protection against the onset of the high-pressure neurological syndrome. Lithium had a protective effect against nitrogen-narcosis and losartan reduced cardiac changes in repetitive diving. Human studies showed no beneficial or dangerous pressure-related interactions. In prevention of diving disorders, pseudoephedrine reduced otic barotrauma, vitamins C and E reduced endothelial dysfunction after bounce diving and hepatic oxidative stress in saturation diving.

Discussion and conclusions: Animal studies revealed that psycho-pharmaceuticals can limit the onset of neurologic symptoms and cardiovascular protective drugs might add a potential protective effect against decompression sickness. No evidence of significant risks due to changes in pharmacologic mechanisms were revealed and most medication is not a contraindication to diving. For improving decision making in prescribing medicine for recreational and occupational divers and to enhance safety by increasing our understanding of pharmacology in hyperbaric conditions, future research should focus on controlled human studies.

Introduction

Scuba diving is an increasingly popular sport with more than 15 million divers worldwide completing more than 250 million dives per year.¹ Certification for scuba diving can be obtained through diving certification organizations. These include, for example, the Professional Association of Diving Instructors (PADI) and Scuba Schools International (SSI). This certification typically involves online classes, classroom instruction, pool practice and open-water training. Since physiological changes are induced by immersion, swimming

and using special equipment during diving, divers must be fit to dive.^{2,3} The laws of physics that are important to take into consideration while diving are Boyle's law, Henry's law and Dalton's law. These laws provide explanations for the possible occurrences of barotrauma, decompression sickness (DCS), nitrogen narcosis and oxygen toxicity, amongst other pathophysiological impacts of the underwater environment.⁴ Although the hazards of diving are principally identical for sport, commercial and military divers, the risks may vary depending on the varying diving procedures and equipment used. Appropriate training, skills and equipment can aid in

reducing the risk of diving and, depending on jurisdictions, regular medical assessment is required before diving.

Medical disorders or use of medication may have an impact on the capacity to adapt to hyperbaric conditions and could affect medical fitness to dive.⁵ Illnesses, such as asthma or epilepsy, require a medical clearance. However, in most cases, evidence of causality is absent and it is not always straightforward to predict the effect of medication on cognitive and physical functioning in hyperbaric conditions. General health, specifics of the disorder, medication interaction and the hyperbaric conditions are all factors in this assessment process. Obviously, regulations concerning commercial divers are stricter, and illnesses concerning a diving career are a stronger contraindication than onset during a diving career. Many protocols have been written for selecting humans for work under hyperbaric conditions or (recreational) diving, however robust evidence to guide practice is limited.⁶⁻⁷

The primary aim of this systematic review of the current human and animal study literature was to assess the interactions between the hyperbaric environment and medications. The secondary aim was to provide a heuristic approach to support decision making regarding physical fitness for occupational health under hyperbaric conditions and (recreational) diving.

Methods

PROTOCOL

The protocol for objectives, literature search strategies, inclusion and exclusion criteria and outcome measurements was prepared *a priori*, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)⁸ statement and is described in this section.

LITERATURE SEARCH STRATEGY

This systematic review sought human and animal studies investigating pharmacodynamic/kinetic effects of the hyperbaric environment on medications or the effects of medications used while diving on the risk of diving disorders. An electronic database search of PubMed, Medline, Embase Science Citation Index Expanded, the Web of Science and World Wide Web search (key words 'scuba diving', 'hyperbaric', 'medication', 'drugs') was performed up to 16 February 2018. These databases were searched for articles published using the medical subject headings (MeSH) or entry terms from Table 1. We focused on the disease entities and most common pharmacological agents. Studies pertaining to the treatment of decompression sickness (DCS), oxygen toxicity and hyperbaric oxygen therapy were excluded from this review because of the different objectives and subject inclusion methods of these studies.

The reference lists from the included studies were searched

Table 1
Search PUBMED

('Diving' [MeSH] OR 'dive' [tw] OR 'diving' [tw] OR 'diver' [tw] OR 'divers' [tw] OR 'scuba' [tw] OR 'hyperbaric' [tw] OR 'deep sea' [tw] OR 'aquanaut' [tw] OR 'aquanauts' [tw] OR 'frogman' [tw] OR 'frogmen' [tw]) AND 'Drug Therapy' [MeSH] OR 'drug' [tw] OR 'drugs' [tw] OR 'medication' [tw] OR 'medications' [tw] OR 'Pharmacological Actions Category' [MeSH] OR 'Pharmaceutical Preparations' [Mesh] OR 'pharmaceuticals' [tw] OR 'medicament' [tw] OR 'medicaments' [tw] OR 'pharmacological' [tw])

to identify additional studies. Two authors (TCFvD, EH) independently identified the studies for inclusion and exclusion and extracted the data. Any inconsistencies between the authors were discussed until consensus was reached. The accuracy of the extracted data was further confirmed by the senior author (RAvH).

QUALITY ASSESSMENT

Studies were rated on the level of evidence provided according to criteria by the Centre for Evidence Based Medicine in Oxford. The methodological quality of observational comparative studies was assessed by the modified Newcastle-Ottawa Scale.^{9,10}

Results

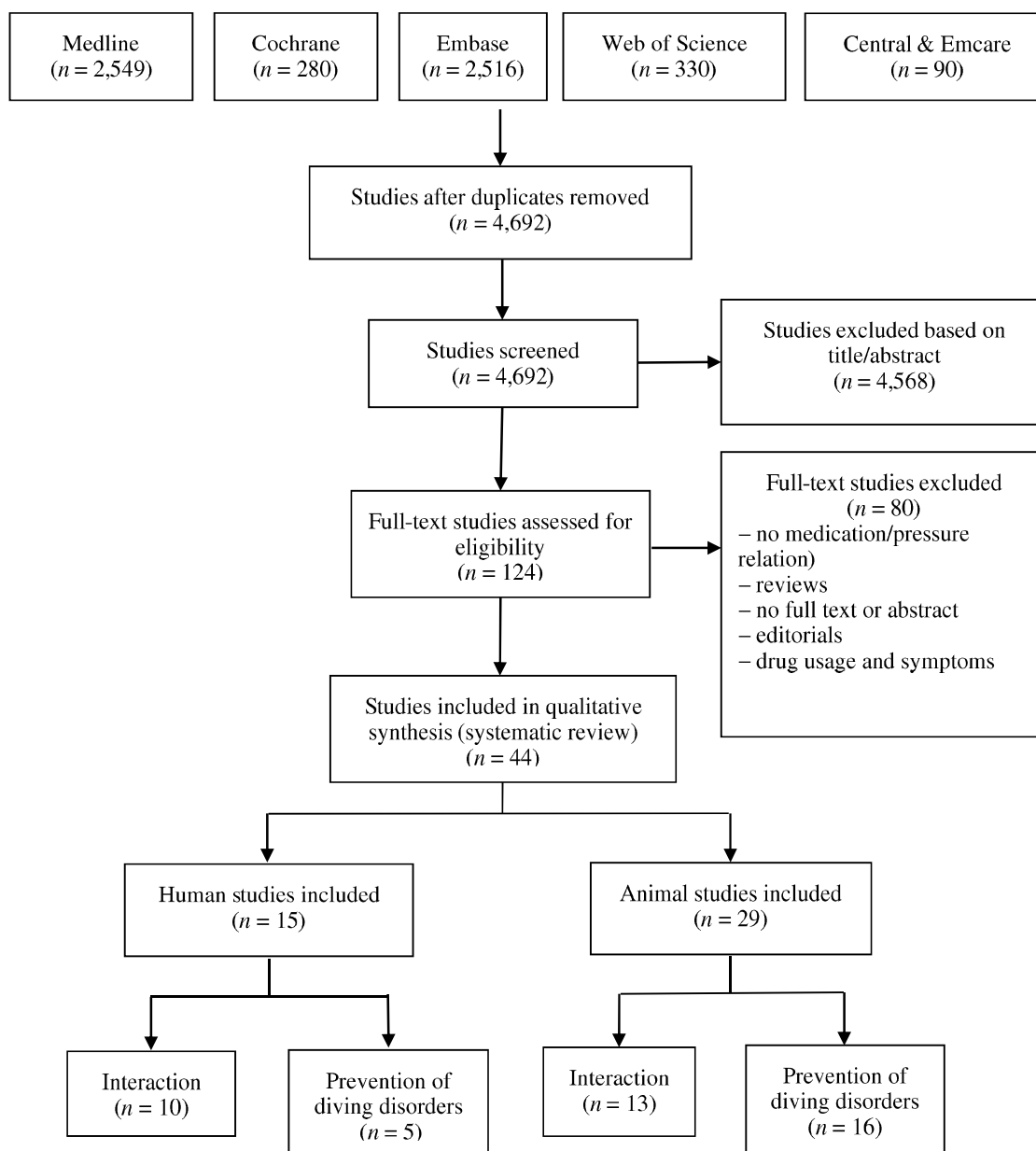
PRISMA FLOWCHART

The PRISMA flowchart quantitatively illustrates the search through to the final studies included in this review (Figure 1). The 44 included studies were subdivided between human and animal studies and further subdivided into two topics, being (1) medication and hyperbaric interaction, and (2) prevention of diving disorders.

MEDICATION AND HYPERBARIC INTERACTION

Table 2 shows the results of the human studies concerning interaction of drugs and hyperbaric pressure. Pharmacologic agents studied were aspirin, dipyridamole, scopolamine, clemastine, pseudoephedrine, dimenhydrinate, cyclizine, oral contraceptives, bleomycin and psychotropic drugs. Aspirin and dipyridamole accounted for some beneficial physiologic changes at a cellular level (preservation of platelet numbers) compared to a placebo following saturation dives.^{11,12} No pressure-related interactions were found. No significant effects on diver performance from transdermal scopolamine were seen. Aggravation of mild symptoms of dry mouth and blurred vision compared to placebo was reported.^{13,14} Dimenhydrinate adversely effected mental flexibility at depth.¹⁵ Cyclizine had a potential small adverse effect on grammatical reasoning, which is increased at depth, but had no effect on a manual task.¹⁶ These effects on various aspects

Figure 1
Literature search flow chart on the effects of medications under hyperbaric conditions



of diver performance, especially at depth, could possibly contribute to cyclizine worsening the risks of diving.¹⁷ For all other agents studied, no beneficial or dangerous direct pressure-related interactions were found.¹⁸⁻²¹

Several animal studies showed significant beneficial effects of pharmacologic agents when animals were exposed to hyperbaric conditions (Table 3). Diazepam and valproate reduced the severity of the high-pressure nervous syndrome (HPNS) at depths beyond 150 metres' sea water (msw) in rats and baboons.^{22,23} Lithium provided some protection against nitrogen narcosis in rats.²⁴ Lastly, losartan prevented deleterious changes in cardiac function seen after repeated hyperbaric exposures in rats.²⁵

Conversely, some studies showed significant adverse effects. Sildenafil use showed an increased incidence of DCS combined with an exacerbated reduction in platelet numbers after hyperbaric exposure.²⁶ The antibiotics benzyl-penicillin, gentamycin and rifampicin were less effective at simulated depth.^{27,28} Finally, lithium significantly potentiated the onset and severity of HPNS symptoms.²⁴ Studies of the use of salicylate, theophylline, meperidine, pentobarbital, and non-competitive N-methyl-D-aspartate receptor (NMDA) receptor antagonists did not show an interaction between the pharmacologic agents and the hyperbaric environment.²⁹⁻³⁴

Table 2

Interaction of hyperbaric pressure and the use of pharmacologic agents in human studies; ATA – atmospheres absolute pressure; DCT – decompression time; LoE – level of evidence; MTC – mega thrombocyte; *n* – number; OW(HL) – open water (Hydrolab); PC – pressure chamber; RBC – red blood cell count; resp – respiratory; VK744 – analogue of dipyridamole

Reference	<i>n</i>	Drug	Control	Pressure (ATA)	Bottom time	Location	Blinded	Outcome	Results	LoE
12	20	Aspirin	Placebo	2.4	60 h	OW(HL)	Yes	Platelet count	Reduced platelets in control group	Ib
12	12	VK744 (dipyridamole)	Placebo	2.4	5 days (incl. DCT)	OW(HL)	Yes	Platelet count	Greater elevation of MTC in VK744; reduced platelets in control group	Ib
11	24	Aspirin; Dipyridamole	Placebo	2.8	48 h	PC	Yes	Platelet count and function	Reduced platelets in dipyridamole and control groups	Ib
13	10	Scopolamine	Placebo	2.8	5.5 days	PC	Yes	Cognitive	No significant effects	Ib
14	24	Scopolamine	Placebo	4.8	11 min	PC	Yes	Cognitive	No significant effects	Ib
21	102	Clemastine fumarate	Placebo	6.1	20 min	PC	Yes	Cognitive	No significant effects	Ib
15	30	Pseudoephedrine; Dimenhydrinate	Placebo	3.0	30 min	PC	Yes	Cognitive	Pseudoephedrine nil effects; dimenhydrinate reduced performance	Ib
17	24	Pseudoephedrine; Cyclizine	Placebo	4.0	5 min	PC	Yes	Cognitive	Pseudoephedrine nil effects; cyclizine reduced performance	Ib
18	30	Oral contraceptives	None	3.5	25 min	OW	No	Bubble production	No differences	IV
19	1	Bleomycin	None	Multiple	Multiple	OW	No	Resp. distress or fatigue	No complications	V
20	1,608	Psychotropic drugs	None (survey)	Multiple	Unknown	OW	No	Narcosis (severe)	No significant effects	IIb

Table 3

Interaction of hyperbaric pressure and the use of pharmacologic agents in animal studies; ATA – atmospheres absolute pressure; I ATA – control group had drug but remained at 1 ATA; * denotes an additional control group without drug but at test pressure; ; DCS – decompression sickness; EC – Escherichia coli; He – helium; HPNS – high-pressure nervous syndrome; LoE – level of evidence; MIC – minimum inhibitory concentration; MK-801 – dizocilpine; n – number; N₂ – nitrogen; NA – not applicable; NR – not reported; PC – pressure chamber; PCP – phenacyclidine; SA – Staphylococcus aureus; Salm – Salmonella sp; SKF – alazocine; U – unknown

Reference	n	Type	Drug	Control (ATA)	Pressure (ATA)	Bottom time (h)	Location	Blinded	Outcome	Results	LoE
29	138	Rats	Salicylate	1*	9	3.5	PC	Yes	Anti-pyretic effect	No interaction	Ib
28	U	SA, EC	Antibiotics	1	Multiple	16	OW	N/A	Antibiotic efficacy	Increased MIC; penicillin for SA	IIb
24	40	Rats	Lithium	1*	19.2	NR	PC	Yes	N ₂ narcosis HPNS	Reduced narcosis; potentiation of HPNS	Ib
22	78	Rats	Diazepam	1	90	2.5	PC	NR	Anesthetic and anticonvulsive effect; HPNS	Prevention of convulsion; reduction of HPNS	IIb
30	U	Dogs	Theophylline	1	6	U	PC	No	Pharmacokinetics	No changes	IIb
31	U	Dogs	Meperidine	1	6	U	PC	No	Pharmacokinetics	No changes	IIb
33	U	Dogs	Pentobarbital	1	6	U	PC	No	Pharmacokinetics	No changes	IIb
32	U	Dogs	Salicylate	1	6	U	PC	No	Pharmacokinetics	Increased clearance at 2.8 ATA and 100% O ₂	IIb
23	8	Baboons	Sodium valproate	* only	61	5	PC	Yes	Effect on HPNS	Reduced severity	Ib
34	25	Rats	NMDA antagonists	1*	till onset HPNS	several	PC	NR	Effect on HPNS	Little or no effect	Ib
27	U	SA, EC, Salm.	Antibiotics	1	36; 71	18	PC	N/A	Antibiotic efficacy	Increased MIC; penicillin for SA; gentamycin and rifampicin for EC + Salm	IIb
25	19	Rats	Losartan	1*	5	30 min x 40 d	PC	NR	Cardiac function	Prevention of change	Ib
26	67	Mice	Sildenafil	* only	10.2	45 min	PC	Yes	DCS	Increased incidence	Ib

Table 4 Effects of pharmacologic agents in prevention of diving disorders in human studies; ATA – atmospheres absolute pressure; LoE – level of evidence; n – number; OW(HL) – open water (hydro lab); PC – pressure chamber; Vit – vitamin

Reference	n	Drug	Control	Pressure (ATA)	Bottom time	Location	Blinded	Outcome	Results	LoE
35	116	Pseudoephedrine	Placebo	2.2	Several dives	PC	Yes	Otologic symptoms	Lower TEED score, less discomfort and blockage	Ib
39	15	Vitamin C and E	Placebo	1.4	30 min	OW	Yes	Eustachian tube function	No difference	Ib
38	10	Vitamin C and E tea catechins	None	41	30 days	PC	No	Oxidative stress (liver function)	Less oxidative stress	IIIb
36	6	Vitamin C and E	Placebo	4.0	36 min	OW	Yes	Endothelial/cardiac function	Reversal of brachial artery endothelial dysfunction	Ib
37	16	Statins	Placebo	2.8	80 min	PC	Yes	Bubble formation	No difference	Ib

PHARMACOLOGICAL AGENTS IN PREVENTION OF DIVING DISORDERS

In human studies investigating protective effects of medications on diving disorders, pseudoephedrine, the anti-oxidants vitamin C and E and statins were tested (Table 4). The use of pseudoephedrine resulted in fewer otologic barotrauma symptoms in comparison to placebo.³⁵ In one study vitamins C and E showed reversal of brachial artery endothelial dysfunction, potentially diminishing bubble formation.³⁶ Statins did not reduce post-dive bubble formation.³⁷ Antioxidants (vitamins C, E and tea catechins) reduced hepatic oxidative stress in saturation diving,³⁸ but the same vitamins did not improve eustachian tube function after oxygen dives.³⁹

Table 5 shows the results of pharmacologic DCS prevention in animal studies. When used before hyperbaric exposure, clopidogrel,⁴⁰ cyproheptadine,⁴¹ dimethothiazine,⁴² aspirin and levodopa,⁴³ and escin⁴⁴ showed a significant reduction of mortality and incidence of DCS. Combined use of aspirin with levodopa had an added beneficial effect. A significantly decreased incidence of DCS and reduction of symptoms was seen with fluoxetine, abciximab, hydrogen enriched saline and simvastatin.^{45–48} A beneficial effect on DCS symptoms was seen also with dibutyl cAMP⁴⁹ and cyclohexanone (with decompression beyond normobaric pressure to an equivalent of 26,000 feet).⁵⁰ Pre-treatment with terbutaline, heparin, superoxide dismutase, catalase or amphetamine exhibited no relevant effects.^{51–53} The anti-depressant spadin, a sortilin-derived peptide, was the only medication that showed a negative effect in a simulated diving study, with increased susceptibility to neurologic DCS symptoms.⁵⁴

Discussion

GENERAL

Animal studies revealed that slight benefits might be expected from some psychopharmaceutic agents against the onset of HPNS symptoms.^{22–24} Also, several cardiovascular drugs could add a potential protective effect against DCS.^{40,43,46,48} However, these pharmacologic agents were tested on small mammals. Studies using dogs were specifically aimed at pharmacokinetics of drugs under hyperbaric conditions.^{30–33} Apart from an increased clearance of salicylate at depth, these studies did not reveal significant pharmacokinetic changes due to hyperbaric conditions. In contrast to the protective effect of theophylline found in guinea pigs,⁵⁵ a study in dogs showed that the use of a bronchodilator (aminophylline) before venous infusion of microbubbles resulted in an increased passage of these microbubbles across the pulmonary microvasculature.⁵⁶

Studies of effects of pharmacological agents in hyperbaric conditions in humans are scarce. This is not surprising given the ethical considerations. Available studies showed few major effects of pharmacological agents in hyperbaric

Table 5

Effects of pharmacologic agents on DCS prevention in animal studies; ATA – atmospheres absolute pressure; 1 ATA – control group had drug but remained at 1 ATA; * denotes an additional control group without drug but at test pressure; PC – pressure chamber; DCS – decompression sickness; fb – followed by; ft – feet; H₂ – hydrogen; LoE – Level of Evidence; n – number; N/A – not applicable; NR – not reported; PC – pressure chamber; SOD – superoxide dismutase; RBC – red blood cell; SOD – superoxide dismutase; W/D ratio – wet/dry ratio

Reference	n	Type	Drug (group)	Control (ATA)	Pressure (ATA)	Bottom time	Location	Blinded	Results	LoE
55	138	Guinea pigs	Theophylline	* only	7.4	60 min	PC	Yes	50% mortality reduction (100% combined with 100% O ₂)	Ib
50	110	Mice	Cyclohexanone	1*	6.3 fb 26,000 ft	6 h	PC	NR	Protective effect	Ib
42	200	Mice	Dimetotiazine	* only	6.3	6 h	PC	NR	Reduced mortality, manifestations and pathologic changes	Ib
51	7	Rabbits	Terbutaline	* only	2 fb 39,000 ft	NR	PC	NR	Reduced incidence	IV
41	500	Mice	Cyproheptadine	* only	6.3	6 h	PC	NR	Reduced mortality, manifestations and pathologic changes	Ib
53	64	Mice	Amphetamine + cyproheptadine	1*	6.3	6 h	PC	NR	No additive effect of amphetamine combined with cyproheptadine	IIb
43	202	Rats	Levodopa + aspirin	* only	7.0	30 min	PC	NR	Reduced incidence and mortality enhanced with combined therapy	Ib
52	44	Dogs	Heparin; SOD; catalase	1*	10	≥10 min	PC	NR	No effect	Ib
49	45	Rats	Dibutyryl cAMP	1*	6.3 / 7.0	120 / 60 min	PC	NR	Reduced inflammation and pulmonary oedema	Ib
47	84	Rats	H ₂ -enriched saline	1*	7.1	90 min	PC	NR	Reduced incidence	Ib
45	91	Mice	Fluoxetine	1*	10.2	45 min	PC	Yes	Reduced incidence and better neurological recovery; reduced loss of platelets and RBCs	Ib
40	111	Rats	Clopidogrel	1*	16.3	270 s	PC	NR	Reduced mortality and inflammatory lung injury	Ib
46	80	Mice	Antiplatelet drugs	1*	9.2	45 min	PC	NR	Reduced incidence with abciximab.	Ib
48	NR	Rats	Simvastatin	* only	7.1	100 min	PC	NR	Reduced incidence and inflammatory lung injury	Ib
54	280	Mice	Fluoxetine; spadin	1*	9.0	45 min	PC	NR	Fluoxetine protective; spadin increased susceptibility	Ib
44	90	Rats	Escin	* only	7	90 min	PC	Yes	Reduced incidence and mortality	Ib

conditions. Most evidence was gained through animal experiments with often extreme diving profiles (to provoke bubble formation). Extrapolation of animal studies to humans should be done with caution.⁵⁷

Human studies are needed to examine whether the medications or vitamins used in the animal studies will have beneficial or harmful effects for healthy divers in wet circumstances. Besides the pharmacological effect, diving with medication affecting cardiovascular responses should be undertaken cautiously, lest there be unintended effects on life-threatening conditions such as immersion pulmonary oedema.^{58–60} Immersion alters the balance between the sympathetic and parasympathetic nervous systems, thus affecting the responses to many physiological processes.^{61,62} However, most research was conducted in recompression chambers, where subjects are exposed to hyperbaric pressure without immersion in water. These so called ‘dry-dives’ simulate hyperbaric conditions and accompanying hyperoxia or increased uptake of inert gases, but do not simulate immersion, hypothermia or the increased workload of fin swimming. Results from dry-dives should be interpreted cautiously when assessing the effects of pharmacologic interventions in scuba diving.

FITNESS TO DIVE

The primary aim of this systematic review was the assessment of available evidence on the effects of hyperbaric circumstances on use of medication, thereby enhancing heuristics supported by evidence-based medicine in the assessment of fitness to dive. Based on the outcomes of this study, being physically fit to dive remains the cornerstone of medical diving clearance. This judgment is often based on assumptions and risk analysis, when the risk is not easily assessed. In the medical examination of a diver, an understanding of the effects of medication, the disease being treated and the impact that the hyperbaric environment might have on both is essential. Any serious symptoms of illness or side effects of medication under normobaric circumstances are potentially a valid reason for rejection.

ENVIRONMENTAL AND HYPERBARIC CONDITIONS

Environmental conditions during a dive vary enormously, from relaxed scuba diving in calm, warm, shallow tropical waters, to professional divers at extreme depth for several weeks (i.e., saturation diving). Conditions can deteriorate rapidly, caused by change in the environment (waves, currents), technical apparatus malfunctions or problems with a diving buddy. In all these situations it becomes a challenge to adapt oneself physically and mentally to the new circumstances.

Apart from diving medical clearance, an individual diver should answer the following key questions before every dive:

- Is my physical condition sufficient to cope with the required strain?

- Am I mentally prepared to cope with the demanding situation?
- Do I (and my buddy) possess the skills for this activity?

Thus, a tailored assessment that encompasses more than medical conditions and medications is required. A diving medical clearance which imposes depth limitations is unjustified as circumstances can change rapidly.

LIMITATIONS

To our knowledge, this is the first systematic review focusing on the effects of the hyperbaric environment on medication, and the effects of medication on diving disorders. However, any conclusions are substantially limited by the poor quality of the available evidence. According to the Quality Assessment there is a risk of bias in most of the included animal studies. Also, protocols vary between studies, making it harder to compare them in a meta-analysis. Different hyperbaric pressures or lengths of exposure might influence the outcome. Furthermore, most studies used dry dives, whilst immersion is essential for a proper judgement of the effects of medication on safety during diving.

Conclusion

This systematic review revealed no evidence of significant risks due to changes in pharmacologic mechanisms in the hyperbaric environment. However, it is unlikely that hyperbaric conditions diminish any risks of medication encountered in non-hyperbaric conditions. Regarding prevention or treatment of DCS, pharmacologic agents targeted at cardiovascular diseases like aspirin, losartan, clopidogrel or simvastatin could add a potential protective effect although evidence is limited. The anti-depressant fluoxetine may also warrant further investigation. For decision making in prescribing medicine for recreational and occupational divers and to enhance safety by increasing our understanding of pharmacy and diving, future research should focus on human studies in submersed circumstances.

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