



**HAL**  
open science

# The effect of Zolpidem on cognitive function and postural control at 3800 m: a cross-over double blind randomized study

Guillaume Sechaud

► **To cite this version:**

Guillaume Sechaud. The effect of Zolpidem on cognitive function and postural control at 3800 m: a cross-over double blind randomized study. Human health and pathology. 2017. dumas-03087219

**HAL Id: dumas-03087219**

**<https://dumas.ccsd.cnrs.fr/dumas-03087219>**

Submitted on 23 Dec 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



## AVERTISSEMENT

Ce document est le fruit d'un long travail approuvé par le jury de soutenance et mis à disposition de l'ensemble de la communauté universitaire élargie.

Il n'a pas été réévalué depuis la date de soutenance.

Il est soumis à la propriété intellectuelle de l'auteur. Ceci implique une obligation de citation et de référencement lors de l'utilisation de ce document.

D'autre part, toute contrefaçon, plagiat, reproduction illicite encourt une poursuite pénale.

Contact au SID de Grenoble :  
[bump-theses@univ-grenoble-alpes.fr](mailto:bump-theses@univ-grenoble-alpes.fr)

## LIENS

Code de la Propriété Intellectuelle. articles L 122. 4

Code de la Propriété Intellectuelle. articles L 335.2- L 335.10

<http://www.cfcopies.com/juridique/droit-auteur>

<http://www.culture.gouv.fr/culture/infos-pratiques/droits/protection.htm>

UNIVERSITÉ GRENOBLE ALPES  
FACULTÉ DE MÉDECINE DE GRENOBLE

Année : 2017

N°

**Effets d'une prise unique de 10mg de zolpidem en haute altitude (3800m) sur les performances cognitives et posturales :  
essai randomisé contrôlé contre placebo en *cross-over* et double aveugle.**

THÈSE  
PRÉSENTÉE POUR L'OBTENTION DU DOCTORAT EN MÉDECINE  
DIPLOME D'ÉTAT

Mr Guillaume SECHAUD

[Données à caractère personnel]

THÈSE SOUTENUE PUBLIQUEMENT A LA FACULTÉ DE MÉDECINE DE GRENOBLE\*

Le 01 décembre 2017

Devant le jury composé de :

Président du jury : Mr. le Pr Jean-François PAYEN DE LA GARANDERIE

Directeur de thèse : Mr. le Pr Pierre BOUZAT

Co-directeur de thèse : Mr. le Dr Samuel VERGES

Membres : Mr. le Pr Pierre ALBALADEJO

Mr. le Dr Paul ROBACH

*\*La Faculté de Médecine de Grenoble n'entend donner aucune approbation ni improbation aux opinions émises dans les thèses ; ces opinions sont considérées comme propres à leurs auteurs.*

Doyen de la Faculté : Pr. Jean Paul ROMANET

Année 2017-2018

ENSEIGNANTS A L'UFR DE MEDECINE

CORPS	NOM-PRENOM	Discipline universitaire
PU-PH	ALBALADEJO Pierre	Anesthésiologie réanimation
PU-PH	APEL Florent	Ophthalmologie
PU-PH	ARVIEUX-BARTHELEMY Catherine	Chirurgie générale
PU-PH	BAILLET Athan	Rhumatologie
PU-PH	BARONE-ROCHETTE Gilles	Cardiologie
PU-PH	BAYAT Sam	Physiologie
PU-PH	BENHAMOU Pierre Yves	Endocrinologie, diabète et maladies métaboliques
PU-PH	BERGER François	Biologie cellulaire
MCU-PH	BIDART-COUTTON Marie	Biologie cellulaire
MCU-PH	BOISSET Sandrine	Agents infectieux
PU-PH	BONAZ Bruno	Gastro-entérologie, hépatologie, addictologie
PU-PH	BONNETERRE Vincent	Médecine et santé au travail
PU-PH	BOREL Anne-Laure	Endocrinologie, diabète et maladies métaboliques
PU-PH	BOSSON Jean-Luc	Biostatistiques, informatique médicale et technologies de communication
MCU-PH	BOTTARI Serge	Biologie cellulaire
PU-PH	BOUGEROL Thierry	Psychiatrie d'adultes
PU-PH	BOUILLET Laurence	Médecine interne
PU-PH	BOUZAT Pierre	Réanimation
MCU-PH	BRENIER-PINCHART Marie Pierre	Parasitologie et mycologie
PU-PH	BRICAULT Ivan	Radiologie et imagerie médicale
PU-PH	BRICHON Pierre-Yves	Chirurgie thoracique et cardio-vasculaire
MCU-PH	BRIOT Raphaël	Thérapeutique, médecine d'urgence
MCU-PH	BROUILLET Sophie	Biologie et médecine du développement et de la reproduction
PU-PH	CAHN Jean-Yves	Hématologie
PU-PH	CARPENTIER Françoise	Thérapeutique, médecine d'urgence
PU-PH	CARPENTIER Patrick	Chirurgie vasculaire, médecine vasculaire
PU-PH	CESBRON Jean-Yves	Immunologie
PU-PH	CHABARDES Stephan	Neurochirurgie
PU-PH	CHABRE Olivier	Endocrinologie, diabète et maladies métaboliques
PU-PH	CHAFFANJON Philippe	Anatomie
PU-PH	CHARLES Julie	Dermatologie
PU-PH	CHAVANON Olivier	Chirurgie thoracique et cardio-vasculaire
PU-PH	CHIQUET Christophe	Ophthalmologie

PU-PH	<b>CHIRICA Mircea</b>	<b>Chirurgie générale</b>
PU-PH	<b>CINQUIN Philippe</b>	<b>Biostatistiques, informatique médicale et technologies de communication</b>
MCU-PH	<b>CLAVARINO Giovanna</b>	<b>Immunologie</b>
PU-PH	<b>COHEN Olivier</b>	<b>Biostatistiques, informatique médicale et technologies de communication</b>
PU-PH	<b>COURVOISIER Aurélien</b>	<b>Chirurgie infantile</b>
PU-PH	<b>COUTURIER Pascal</b>	<b>Gériatrie et biologie du vieillissement</b>
PU-PH	<b>CRACOWSKI Jean-Luc</b>	<b>Pharmacologie fondamentale, pharmacologie clinique</b>
PU-PH	<b>CURE Hervé</b>	<b>Oncologie</b>
PU-PH	<b>DEBILLON Thierry</b>	<b>Pédiatrie</b>
PU-PH	<b>DECAENS Thomas</b>	<b>Gastro-entérologie, Hépatologie</b>
PU-PH	<b>DEMATTEIS Maurice</b>	<b>Addictologie</b>
MCU-PH	<b>DERANSART Colin</b>	<b>Physiologie</b>
PU-PH	<b>DESCOTES Jean-Luc</b>	<b>Urologie</b>
MCU-PH	<b>DETANTE Olivier</b>	<b>Neurologie</b>
MCU-PH	<b>DIETERICH Klaus</b>	<b>Génétique et procréation</b>
MCU-PH	<b>DOUTRELEAU Stéphane</b>	<b>Physiologie</b>
MCU-PH	<b>DUMESTRE-PERARD Chantal</b>	<b>Immunologie</b>
PU-PH	<b>EPAULARD Olivier</b>	<b>Maladies Infectieuses et Tropicales</b>
PU-PH	<b>ESTEVE François</b>	<b>Biophysique et médecine nucléaire</b>
MCU-PH	<b>EYSSERIC Hélène</b>	<b>Médecine légale et droit de la santé</b>
PU-PH	<b>FAGRET Daniel</b>	<b>Biophysique et médecine nucléaire</b>
PU-PH	<b>FAUCHERON Jean-Luc</b>	<b>Chirurgie générale</b>
MCU-PH	<b>FAURE Julien</b>	<b>Biochimie et biologie moléculaire</b>
PU-PH	<b>FERRETTI Gilbert</b>	<b>Radiologie et imagerie médicale</b>
PU-PH	<b>FEUERSTEIN Claude</b>	<b>Physiologie</b>
PU-PH	<b>FONTAINE Éric</b>	<b>Nutrition</b>
PU-PH	<b>FRANCOIS Patrice</b>	<b>Epidémiologie, économie de la santé et prévention</b>
MCU-MG	<b>GABOREAU Yoann</b>	<b>Médecine Générale</b>
PU-PH	<b>GARBAN Frédéric</b>	<b>Hématologie, transfusion</b>
PU-PH	<b>GAUDIN Philippe</b>	<b>Rhumatologie</b>
PU-PH	<b>GAVAZZI Gaétan</b>	<b>Gériatrie et biologie du vieillissement</b>
PU-PH	<b>GAY Emmanuel</b>	<b>Neurochirurgie</b>
MCU-PH	<b>GILLOIS Pierre</b>	<b>Biostatistiques, informatique médicale et technologies de communication</b>
MCU-PH	<b>GRAND Sylvie</b>	<b>Radiologie et imagerie médicale</b>
PU-PH	<b>GRIFFET Jacques</b>	<b>Chirurgie infantile</b>
PU-PH	<b>GUEBRE-EGZIABHER Fitsum</b>	<b>Néphrologie</b>
MCU-PH	<b>GUZUN Rita</b>	<b>Endocrinologie, diabétologie, nutrition, éducation thérapeutique</b>
PU-PH	<b>HAINAUT Pierre</b>	<b>Biochimie, biologie moléculaire</b>
PU-PH	<b>HENNEBICQ Sylviane</b>	<b>Génétique et procréation</b>
PU-PH	<b>HOFFMANN Pascale</b>	<b>Gynécologie obstétrique</b>
PU-PH	<b>HOMMEL Marc</b>	<b>Neurologie</b>
PU-MG	<b>IMBERT Patrick</b>	<b>Médecine Générale</b>
PU-PH	<b>JOUK Pierre-Simon</b>	<b>Génétique</b>
PU-PH	<b>JUVIN Robert</b>	<b>Rhumatologie</b>

PU-PH	<b>KAHANE Philippe</b>	Physiologie
MCU-PH	<b>KASTLER Adrian</b>	Radiologie et imagerie médicale
PU-PH	<b>KRACK Paul</b>	Neurologie
PU-PH	<b>KRAINIK Alexandre</b>	Radiologie et imagerie médicale
PU-PH	<b>LABARERE José</b>	Epidémiologie ; Eco. de la Santé
MCU-PH	<b>LABLANCHE Sandrine</b>	Endocrinologie, diabète et maladies métaboliques
MCU-PH	<b>LANDELLE Caroline</b>	Bactériologie - virologie
MCU-PH	<b>LAPORTE François</b>	Biochimie et biologie moléculaire
MCU-PH	<b>LARDY Bernard</b>	Biochimie et biologie moléculaire
MCU-PH	<b>LARRAT Sylvie</b>	Bactériologie, virologie
MCU - PH	<b>LE PISSART Audrey</b>	Biochimie et biologie moléculaire
PU-PH	<b>LECCIA Marie-Thérèse</b>	Dermato-vénérologie
PU-PH	<b>LEROUX Dominique</b>	Génétique
PU-PH	<b>LEROY Vincent</b>	Gastro-entérologie, hépatologie, addictologie
PU-PH	<b>LEVY Patrick</b>	Physiologie
PU-PH	<b>LONG Jean-Alexandre</b>	Urologie
PU-PH	<b>MAGNE Jean-Luc</b>	Chirurgie vasculaire
MCU-PH	<b>MAIGNAN Maxime</b>	Thérapeutique, médecine d'urgence
PU-PH	<b>MAITRE Anne</b>	Médecine et santé au travail
MCU-PH	<b>MALLARET Marie-Reine</b>	Epidémiologie, économie de la santé et prévention
MCU-PH	<b>MARLU Raphaël</b>	Hématologie, transfusion
MCU-PH	<b>MAUBON Danièle</b>	Parasitologie et mycologie
PU-PH	<b>MAURIN Max</b>	Bactériologie - virologie
MCU-PH	<b>MC LEER Anne</b>	Cytologie et histologie
PU-PH	<b>MERLOZ Philippe</b>	Chirurgie orthopédique et traumatologie
PU-PH	<b>MORAND Patrice</b>	Bactériologie - virologie
PU-PH	<b>MOREAU-GAUDRY Alexandre</b>	Biostatistiques, informatique médicale et technologies de communication
PU-PH	<b>MORO Elena</b>	Neurologie
PU-PH	<b>MORO-SIBILOT Denis</b>	Pneumologie
PU-PH	<b>MOUSSEAU Mireille</b>	Cancérologie
PU-PH	<b>MOUTET François</b>	Chirurgie plastique, reconstructrice et esthétique ; brûlologie
MCU-PH	<b>PACLET Marie-Hélène</b>	Biochimie et biologie moléculaire
PU-PH	<b>PALOMBI Olivier</b>	Anatomie
PU-PH	<b>PARK Sophie</b>	Hémato - transfusion
PU-PH	<b>PASSAGGIA Jean-Guy</b>	Anatomie
PU-PH	<b>PAYEN DE LA GARANDERIE Jean-François</b>	Anesthésiologie réanimation
MCU-PH	<b>PAYSANT François</b>	Médecine légale et droit de la santé
MCU-PH	<b>PELLETIER Laurent</b>	Biologie cellulaire
PU-PH	<b>PELLOUX Hervé</b>	Parasitologie et mycologie
PU-PH	<b>PEPIN Jean-Louis</b>	Physiologie
PU-PH	<b>PERENNOU Dominique</b>	Médecine physique et de réadaptation
PU-PH	<b>PERNOD Gilles</b>	Médecine vasculaire
PU-PH	<b>PIOLAT Christian</b>	Chirurgie infantile
PU-PH	<b>PISON Christophe</b>	Pneumologie

PU-PH	PLANTAZ Dominique	Pédiatrie
PU-PH	POIGNARD Pascal	Virologie
PU-PH	POLACK Benoît	Hématologie
PU-PH	POLOSAN Mircea	Psychiatrie d'adultes
PU-PH	PONS Jean-Claude	Gynécologie obstétrique
PU-PH	RAMBEAUD Jacques	Urologie
PU-PH	RAY Pierre	Biologie et médecine du développement et de la reproduction
PU-PH	REYT Émile	Oto-rhino-laryngologie
PU-PH	RIGHINI Christian	Oto-rhino-laryngologie
PU-PH	ROMANET Jean Paul	Ophthalmologie
PU-PH	ROSTAING Lionel	Néphrologie
MCU-PH	ROUSTIT Matthieu	Pharmacologie fondamentale, pharmaco clinique, addictologie
MCU-PH	ROUX-BUISSON Nathalie	Biochimie, toxicologie et pharmacologie
MCU-PH	RUBIO Amandine	Pédiatrie
PU-PH	SARAGAGLIA Dominique	Chirurgie orthopédique et traumatologie
MCU-PH	SATRE Véronique	Génétique
PU-PH	SAUDOU Frédéric	Biologie Cellulaire
PU-PH	SCHMERBER Sébastien	Oto-rhino-laryngologie
PU-PH	SCHWEBEL-CANALI Carole	Réanimation médicale
PU-PH	SCOLAN Virginie	Médecine légale et droit de la santé
MCU-PH	SEIGNEURIN Arnaud	Epidémiologie, économie de la santé et prévention
PU-PH	STAHL Jean-Paul	Maladies infectieuses, maladies tropicales
PU-PH	STANKE Françoise	Pharmacologie fondamentale
MCU-PH	STASIA Marie-José	Biochimie et biologie moléculaire
PU-PH	STURM Nathalie	Anatomie et cytologie pathologiques
PU-PH	TAMISIER Renaud	Physiologie
PU-PH	TERZI Nicolas	Réanimation
MCU-PH	TOFFART Anne-Claire	Pneumologie
PU-PH	TONETTI Jérôme	Chirurgie orthopédique et traumatologie
PU-PH	TOUSSAINT Bertrand	Biochimie et biologie moléculaire
PU-PH	VANZETTO Gérald	Cardiologie
PU-PH	VUILLEZ Jean-Philippe	Biophysique et médecine nucléaire
PU-PH	WEIL Georges	Epidémiologie, économie de la santé et prévention
PU-PH	ZAOUI Philippe	Néphrologie
PU-PH	ZARSKI Jean-Pierre	Gastro-entérologie, hépatologie, addictologie

**PU-PH** : Professeur des Universités et Praticiens Hospitaliers  
**MCU-PH** : Maître de Conférences des Universités et Praticiens Hospitaliers  
**PU-MG** : Professeur des Universités de Médecine Générale  
**MCU-MG** : Maître de Conférences des Universités de Médecine Générale

# REMERCIEMENTS

---

## **A Messieurs les membres du jury :**

Pr Jean-François Payen, merci d'avoir accepté de juger mon travail, plus physiologique qu'anesthésique ou réanimatoire, ainsi que pour votre présence pour notre formation.

Pr Pierre Albaladejo, merci d'avoir accepté de juger mon travail, après ces 4 années de collaboration pour l'organisation de l'internat et les nombreuses heures à rentrer les données de GIHP-NACO...

Pr Pierre Bouzat, merci d'avoir été impliqué dans ce travail et dans notre formation, tu gardes ton esprit blagueur malgré tes responsabilités grandissantes, c'est toujours agréable de travailler avec toi. Un regret quand même, qui est de n'avoir pu faire aboutir notre premier projet sur le syndrome du harnais...

Paul, merci d'avoir accepté de juger mon travail, après m'avoir accueilli et gérer une bonne partie de la logistique sur Cham.

Samuel, ta soif de projet est impressionnante, merci d'avoir dirigé ce travail, depuis sa création et jusqu'à la publication à venir...

**A tous les sujets de l'étude** ayant accepté de somnambuler dans des états parfois seconds pour les bienfaits de la science.

**Aux partenaires** financiers et organisationnels du projet permettant sa réalisation : EXALT, la Fédération Française des Clubs Alpains de Montagne, la fondation Petzl, la Compagnie du Mont Blanc, l'ENSA, le laboratoire HP2, les universités Aix-Marseille et Grenoble Alpes, le CHUGA, l'INSERM et le CNRS.

## **Aux membres de ma famille :**

*Mes parents ;* merci d'avoir toujours été derrière nous, d'avoir fait en sorte que nous puissions réussir. Yo, tu nous as transmis ta passion du ski (et ne pas arriver à dépasser le maître, c'est vraiment frustrant !), tu nous as fait bricoler (pardonne nous d'avoir défoncé tes limes à vouloir poncer du bois et tes tournevis à vouloir tailler des pierres !), tu m'as donné le goût du travail, tu m'as emmené dès le plus jeune âge en montagne puis en vélo... merci. Maman, toujours stricte, parfois dure, une fois injuste, tu m'as transmis ta rigueur. Tu as toujours veillé sur nous et proposé des activités et découvertes, égayé notre curiosité. Loin d'avoir hérité de ton sens du ménage, j'ai peut-être trouvé d'où je tiens mes difficultés de rangement. Tu nous as transmis l'envie de réaliser nos confitures, jus et conserves, c'est un régal et c'est à ma portée de « cuisinier »... merci.

*Mes grands-parents paternels ;* Christiane tu nous as donné goût à la musique puis appris le piano, ton unique passion. Tu n'as jamais manqué d'idées pour faire des petites conneries, depuis ton plus jeune âge. Tu disparais un poil trop tôt pour voir aboutir mes « si longues études » comme tu disais, tu aurais voulu voir ça, je n'ai pas été assez rapide. Albert, que des regrets de n'avoir pu profiter de toi et de ce que tu connaissais. J'ai essayé de prendre soin des Bannettes, loin d'être à la hauteur.



*Mes grands-parents maternels ;* Pépé tu as dû nous maudire un certain nombre de fois en nous voyant courir ou faire du vélo dans le jardin, monter aux arbres fruitiers, couper l'oseille pour donner aux poules... Trop jeune à l'époque pour m'intéresser à ce que tu faisais dans « ton garage », tu t'éteindras malheureusement sans nous transmettre ton immense savoir. Mémé, à la plage le pied dans le sac plastique, un des rares souvenirs de temps passé ensemble puisque je ne pensais qu'à passer mes journées à la ferme plutôt qu'à l'intérieur.

*Mes frères et sœurs ;* Matthieu, riche de ce que tu m'as infligé tu m'as rendu plus fort, profite de la famille que tu as créé avec Lucie. Clément et Romain complètent votre couple avec joie et entrain. Stéphanie, suffisamment proche pour être jumeaux nous nous sommes toujours chamaillés sur la taille, mais trop différents pour s'unir contre notre grand frère. Avec deux grands frères le chemin n'a pas été simple mais tu as trouvé dorénavant ta voie et nous dépasses largement, le temps a du bon...

La Famille Allais, trop tardivement découverte.

Jean-Paul et Martine, Mathieu (Séverine et Louis) et Anaïs, pour votre accueil et tous les moments conviviaux que nous passons ensemble. La cueillette des olives fait dorénavant partie de la fin d'année, apportant son lot de bonne humeur, de travail, de grimpe, de gaulage, de ramassage...

### **A mes amis...**

**...d'enfance :** Yaël et Benjamin, nous avons découvert la vie ensemble. Fred, ta disparition a été comme un coup de tonnerre, je n'oublierai jamais toutes ces après-midi, ces complicités,... soit heureux où tu es maintenant.

**...du secondaire :** Bertrand et Julien pour ces heures passées ballon de rugby en main. Valentin pour la découverte de la vie de lycéen et me trainer à courir. Elsa, Clémence et toute la bande du Maroc...

**...des bans de fac :** Joris pour les sorties vélo et le soutien mutuel de la P1, Nico et Myriam pour les aventures associatives, les colocs du « Manoir » (Simon, Jean, Moumoun et Théo, qu'est-ce qu'on a pu rigoler !), Julien et Claire vous êtes formidables (si vous pouviez revenir dans la région...), les équipes de la Kfet, l'AH et la corpo...

**...de l'internat :** Bat' (Kristina et Astrid maintenant) éternel compagnon de cours, de stage, de grimpe, de ski, d'UT4M... Les plus vieux qui m'ont appris beaucoup (Yvo, Marion, Clo, Perrine, Fanny et TTB ; désolé d'avoir été votre boulet sur mes premières gardes), les moins vieux avec qui l'on passe que du bon temps (Xav, Clém et Delphine vous avez coaché mes débuts, merci ; Lara, Camille, Béné et Manue pour une sortie bière, lac ou montagne ; Pier pour ce que tu m'as fait subir avec ce projet (tu es ma tempête, je suis ton phare, n'oublie pas !). La promo, trop éparpillée au grès des stages (Alex, Romain, Laura, Thib, Jérôme et Jenn, Marinette, Audrey et Flora, Manon, Diégo et Ludo) et les plus jeunes toujours volontaires (Féfé, Manue, Barth...)...

**...de montagne :** Philippe, merci pour m'avoir initié, lancé sur la voie, avec une pensée pour Jean-No trop tôt disparu. Ta volonté de mener tes élèves sur les sommets du bout du monde malgré les contraintes est remarquable. Pascal, pour ma première grande voie, à Presles terrain de jeu mythique, puis Omblèze, Ailefroide et retour à Presles... Sylvain, pour tout ce que tu m'as transmis en alpi, en glace, en canyon ou en grimpe, je pense à toi dans ces moments difficiles, courage. Victor et Ben pour votre encadrement dans les équipes FFCAM. Bertrand, toi qui m'a poussé dans les voies dures, et Claude, seul humain à être capable de boiter sur terre et grimper avec aisance ! Max pour toutes ces belles voies réalisées et ces projets (enfin il faut que je retrouve le niveau), tu es un compagnon idéal, efficace. Xav' biensûr trop peu de temps pour profiter ensemble de la montagne mais tu restes un compagnon sûr et agréable. Lolo et David (même si toi tu vas trop vite), pour ces sorties ski-grimpe-canyon-montagne ou autre, et pour votre engagement dans l'EC montagne (pensées à Coco qui a lancé la machine).

**...du club :** Damien depuis si longtemps en grimpe puis dans toutes les autres activités, Jérém, Cécile, Simon, Jo, Emilie et Nico... La bande de jeunes il y a quelques temps et de vieux maintenant.

**...aux copains,** pour m'avoir validé ;-), votre amitié est un vrai bonheur. Thomas et Laure (donc Elio) toujours motivé pour une sortie sportive ou une soirée jeu. Yannick et Manue (ainsi que votre adorable Chloé) partenaires sportif ou de barbecue. Olivier et Anaïs (et Alice), rugby bière pizza c'est fondamental. Thomas et Pauline, vous êtes un couple formidable malheureusement nos agendas respectifs sont trop remplis pour se voir souvent. Cédricou on n'a jamais trouvé le temps d'aller faire du Kite ensemble, je vais devoir passer par l'UCPA ;-). Séb (et Caro) inlassable pratiquant de canyon, de spéléo ou de montagne.

**...du Beaufortain** pour les bons moments estivaux ou hivernaux. Jacques (et Nadia) pour m'avoir accueilli après notre rencontre en spéléo. Gibus et Christophe les moteurs toujours allumés. Oliv' toujours vaillant quelques soit les conditions. Pierre-Yves et ta radio. Thierry pour tes conseils de ski il y a fort longtemps, l'envie que tu m'as donné en gagnant la Pierra Ment' et les étés au chalet d'alpage.

**... du secours spéléo :** la 3SI (Thierry CT impressionnant de maîtrise, Elise, Tristan et Lionel toujours de bons conseils techniques, Serge compagnon de route, Chloé co-formatrice gestion, François recours informatique...). Oliv', William et Ulysse, trio d'inlassables déconneurs. Le SSF (Jeff, Valou et Eva pour ce voyage mémorable au Brésil, on recommence en 2018 ?).

**...France,** tes histoires de secours montagne ou spéléo sont des trésors et motivent les plus jeunes. Merci de m'avoir accueilli dans le milieu du secours, d'abord spéléo puis montagne. Le relai est compliqué, mais le jeu en vaut la chandelle... Espérons d'être à la hauteur de la tâche.

**...Jean-Pierre,** premier contact au Maroc puis régulièrement à Cham. Merci de m'avoir accueilli pendant les stages à l'ENSA. Merci à Michèle de m'avoir permis d'approcher le globe.

**...Philippe** pour m'avoir suivi, soutenu puis ouvert ton cabinet.

**...de la famille,** Pascal et Marie, Jo et Manu, Pierre et Chantal, Patrick, pour m'avoir vu grandir, accompagné dans quelques aventures, et soutenu de près ou de loin.

### **Aux collègues de travail :**

Je ne peux citer tout le monde mais vous m'avez encadré et supporté pendant ces années, merci pour tout...

... aux équipes soignantes de la RPC, vous m'avez appris les bases de la réanimation.

...à Jean-Marc, Nadine et Françoise pour m'avoir fait découvrir l'Anesthésie. Profitez de votre retraite...

...à l'équipe de RNC pour mon stage et votre confiance lors de mes premières gardes sénior. Gilles merci pour ta pédagogie (« dit donc là... »), Clém pour tes astreintes téléphoniques officieuses de mes toutes premières gardes (chouchou tu es géniale).

...aux équipes du bloc et de la réa d'Annecy, vous êtes formidables. Bruno et Lionel on retourne au ski quand vous voulez... Isa forcément de grosses pensées pour toi. Sylvain que je croise maintenant plus sur le parterre d'une DZ qu'au bloc ;-). Didier et Michel vous êtes impressionnants de connaissances et de bienveillance. Etienne, je n'ai pas osé imiter ton internat mais dieu sait que j'en ai eu envie.

...aux équipes du bloc, de la Mat et de la Réa de Chambé, vous m'avez fait aimer l'anesthésie obstétricale. Téo', tu resteras l'anesthésiste que j'aimerais devenir, calme, gentil et ultra compétent.

...aux équipes de Sud pour m'avoir accueilli externe, interne junior puis interne sénior. Merci Hafid pour ta confiance, Jean-Paul pour ta sérénité sans faille.

...aux équipes de pédiatrie, la diversité rencontrée mais surtout la collaboration médico-chirurgicale et la bonne entente m'a donnée envie de revenir, à très vite...

...aux équipes de la Mat, merci pour la confiance accordée lors de mon stage sénior. Ana, Dominique, Hélène et Edith, votre bienveillance est vraiment appréciable. Sabine on est tous avec toi. A très vite également...

...aux équipes du bloc des urgences, déchocage et bloc thoracique et vasculaire, les derniers stages ne sont pas les plus faciles, il faut trouver le juste milieu entre autonomie et apprentissage. Merci Julien pour ton investissement (passé et à venir ;-)), Jules, Marion et Caro pour votre encadrement, Françoise pour ta gentillesse après toutes ces années passées dans l'arène du 101...

...aux A.R.C.s, qui m'ont vu maintes fois venir squatter le bureau, aides indispensables pour la recherche, toujours quelques bonbons à proposer...

...aux secrétaires, toujours présentes pour nos démarches administratives. Clin d'œil particulier à Jocelyne pour toutes les sollicitations durant 4 ans, profite de ta retraite...

...aux équipes du SAMU 38 pour m'avoir accueilli et fait confiance au cours de ces nombreuses gardes. Espérons que l'on puisse continuer à faire du pré-hospitalier, pour le bien de tous... Merci aux ambulanciers à qui l'on donne notre confiance pour nous mener à bien, pour votre conduite sans faille à toute heure du jour ou de la nuit, bravo ! Merci aux infirmiers qui m'ont appris beaucoup du pré-hospitalier et avec qui la collaboration est indispensable. Pensées récentes à Longo et Véro...

...aux équipes du secours en montagne, rêve puis objectif depuis si longtemps, merci pour votre accueil et votre confiance. Les pilotes biensûr à qui l'on donne notre vie et qui gèrent vraiment, qui ne sont jamais avarés de conseils et de rappels d'informations sur la machine et les techniques ; clin d'œil particulier à Franck pour tes remarques avisées et les biscuits de chalet, Rémi pour ta gentillesse (profite bien au bout du monde), Bruno pour le copain à l'œdème de bouche, Renaud pour ta gestion, Richard pour ta bienveillance. Les M.O.B., compagnons indispensables de vol et complices de treuillage, merci pour vos attentions et conseils. Les secouristes, (du PG ou des CRS je mélange toujours les semaines), merci pour vos conseils en formations, votre aide en secours, et les bons moments passés en montagne, en grimpe ou en spéléo.

...à Valé, petite par la taille mais grande par ta gentillesse, ta générosité, ton art culinaire, ta motivation sportive et ton enthousiasme éternel... Merci de t'accrocher à mon agenda et mes activités, d'avoir supporté les contraintes de l'internat, d'avoir gobé les « cachoux » pour la science (passer deux belles nuits à 4000m, c'est ça la science non ?). Continue comme ça, le meilleur reste à venir et s'offre à nous...

# TABLE DES MATIÈRES :

---

<b>Liste des enseignants à l'UFR de Médecine</b>	Page 2
<b>Remerciements</b>	Page 6
<b>Table des matières</b>	Page 10
<b>Résumé</b>	Page 11
<b>Abstract</b>	Page 12
<b>Introduction</b>	Page 13
<b>Material and Methods</b>	Page 15
Study design	Page 15
Subject selection	Page 15
Data collection	Page 16
<i>Protocol</i>	Page 16
<i>Cognitive tests</i>	Page 16
<i>Postural evaluation</i>	Page 19
<i>Sleep recording</i>	Page 20
<i>Questionnaires</i>	Page 21
<i>Blood sampling and analyses</i>	Page 21
Main outcome	Page 21
Secondary outcomes	Page 22
Sample size calculation	Page 22
Statistical analysis	Page 22
<b>Results</b>	Page 23
Simon cognitive test	Page 23
Duration-production task	Page 24
SpO <sub>2</sub> , heart rate and NIRS	Page 24
Postural evaluation	Page 25
Sleep recording and questionnaires	Page 26
Blood sampling	Page 26
<b>Discussion</b>	Page 27
Cognitive performances	Page 27
Postural evaluation	Page 30
Sleep and symptoms	Page 31
Blood sampling	Page 32
<b>Conclusion</b>	Page 33
<b>Bibliographie</b>	Page 36
<b>Annexes</b>	Page 40
<b>Serment</b>	Page 46

# RESUME

---

Le sommeil est perturbé en haute altitude, motivant les alpinistes à consommer des hypnotiques pour améliorer leur sommeil et leur récupération avant la course du lendemain. Aucune étude n'a à ce jour étudié les éventuels effets résiduels d'une telle prise médicamenteuse lors d'un lever nocturne comme c'est le cas pour la pratique de l'alpinisme en haute montagne.

L'objectif de notre travail a été d'évaluer si une consommation de zolpidem au coucher pouvait être responsable d'une altération des capacités cognitives et posturales au réveil des alpinistes en pleine nuit (environ 4 heures après la prise).

Dans cette étude randomisée en double-aveugle, contrôlée en cross-over, 22 sujets ont été évalués sur 4 nuits, en plaine (Grenoble, 210m) et en haute altitude (Aiguille du midi, 3800m), après une prise de 10mg de zolpidem ou de placebo à 22h. Une polygraphie a été réalisée jusqu'à 1h30. Au réveil, une évaluation posturale a été faite sur plateforme de force. Puis, à 2h, deux tests cognitifs ont été réalisés (tâches de Simon et de production temporelle), au repos et à l'exercice, avec enregistrement simultané de l'oxygénation cérébrale. La présence de symptômes de mal aigu des montagnes, la qualité du sommeil et de l'éveil ont également été évalués par questionnaires.

Le zolpidem induisait une augmentation du temps de réaction dans toutes les conditions ( $407\pm 9\text{ms}$  vs  $380\pm 11\text{ms}$  sous placebo ;  $p<0,001$ ) et du taux d'erreurs sur les essais incongruents ( $10\pm 1\%$  vs  $8\pm 1\%$  ;  $p<0,01$ ) alors que le taux d'erreur des essais congruents n'était pas affecté par le traitement. La variabilité temporelle sous zolpidem était augmentée par rapport au placebo ( $p<0,001$ ). Les paramètres posturaux descriptifs tels que la surface de déplacement du centre de pression ( $236\pm 172\text{mm}^2$  sous zolpidem vs  $120\pm 59\text{mm}^2$  sous placebo ;  $p<0,001$ ) et l'écart-type avant-arrière de la longueur de déplacement du centre de pression ( $4,5\pm 2,2\text{mm}$  vs  $3,3\pm 1,2\text{mm}$  ;  $p=0,002$ ) étaient altérés par le zolpidem. Le zolpidem n'altérait pas les principaux paramètres polygraphiques (IAH et  $\text{SpO}_2$  moyenne,  $p>0,05$ ) et améliorait sommeil ( $p<0,001$ ). Les symptômes de mal aigu des montagnes étaient augmentés sous zolpidem : vertiges ( $p=0,003$ ) et ataxie ( $p=0,004$ ).

Une prise de 10mg de zolpidem au coucher en haute altitude est responsable d'une altération des performances cognitives et posturales au réveil en pleine nuit pouvant être délétère pour l'aisance et la sécurité des alpinistes.

# ABSTRACT

---

Sleep is affected by high altitude (periodic breathing and reduced sleep quality), leading numerous alpinists to consume hypnotics in order to improve sleep efficiency and to recover properly for climbing the next day. While alpinists generally wake-up very early at altitude, no study has so far analyzed the potential residual adverse effects of zolpidem during nocturnal wakening at high altitude.

The objective of our study was to evaluate if zolpidem administration at bedtime could induce significant cognitive and postural impairments at early wakening (4 hours after drug intake).

In a randomized double-blind controlled cross-over study, 22 subjects were evaluated during 2 nights at low altitude (Grenoble, 210 m) and 2 nights at high altitude (Aiguille du midi, 3,800 m), after zolpidem (10 mg) or placebo intake at 22:00 pm. Polygraphic recordings were performed until 1:30 am. After waking-up, postural evaluations were conducted on a force platform. Then at 2:00 am, two cognitive tests were performed (Simon task and duration-production task) at rest and during exercise, with cerebral oxygenation monitoring by near infrared spectroscopy. Symptoms of acute mountain sickness, sleep quality and sleepiness were also assessed by questionnaires.

Zolpidem increased reaction time in all conditions (mean with zolpidem  $407\pm 9$  ms vs mean with placebo  $380\pm 11$  ms;  $p<0.001$ ) and error rate in incongruent trials ( $10.2\pm 1.1\%$  vs  $7.8\pm 0.8\%$ ;  $p<0.01$ ) while error rate in congruent trials was unchanged compared to placebo. A larger increase in cerebral oxygenation during cognitive tasks was observed at rest only. Zolpidem intake increased time perception variability compared to placebo ( $p<0.001$ ). Zolpidem altered postural parameters such as the center of pressure area ( $236\pm 171.5$  mm<sup>2</sup> with zolpidem vs  $119.6\pm 59$  mm<sup>2</sup> with placebo;  $p<0.001$ ) and antero-posterior displacement ( $4.5\pm 2.2$  mm vs  $3.3\pm 1.2$  mm;  $p=0.002$ ). Zolpidem did not affect the main polygraphic parameters (apnea-hypopnea index and mean arterial oxygen saturation;  $p>0.05$ ) but increased sleep quality ( $p<0.001$ ). Zolpidem increased symptoms of acute mountain sickness ( $p<0.001$ ), dizziness ( $p=0.003$ ) and ataxia ( $p=0.004$ ).

Acute zolpidem intake before sleep at high altitude alters cognitive performances and postural control during early wakening which may be deleterious for safety and physical capacities of climbers.

# INTRODUCTION

---

Sleep perturbations are observed at high altitude (e.g. modification of sleep architecture [Ainslie *et al.* 2013; Johnson *et al.* 2010], periodic breathing and central sleep apnea [Anholm *et al.* 1992; Windsor *et al.* 2012; Ainslie *et al.* 2013]). These sleep disturbances are highly prevalent [Hackett *et al.* 2001; Windsor *et al.* 2012] and are considered as one of the symptoms characterizing acute mountain sickness (AMS, according to the Lake Louise Score) [Lake Louise Consensus AMS Score 1991].

Hypnotics have been recommended as a mean to improve sleep at high altitude [Jouanin *et al.* 2009] and alpinists frequently use hypnotics in order to improve sleeping and recovery during sojourn at high altitude. Robach *et al.* [2016] studied drug intake in a large sample of climbers on the Mont-Blanc. It appears that after acetazolamide (used in 20.6% of the individuals), the second category of drugs the most frequently used in this population are hypnotics (found in 12.9% of the individuals) with zolpidem being the main drug (8.4% of the individuals).

Zolpidem is a short-acting nonbenzodiazepine hypnotics that is widely used for treatments of acute and chronic insomnia [Katzung *et al.* 2006]. Previous studies at high altitude suggested that acute and chronic zolpidem intake improves sleep quality in climbers with no effect on nocturnal respiratory parameters and reduces symptoms of AMS without inducing cognitive alteration [Beaumont *et al.* 1996; Beaumont *et al.* 2004; Beaumont *et al.* 2007]. The later data were however collected at waking about 8h after zolpidem administration. Alpinists at high altitude generally wake-up substantially earlier in order to climb in the most appropriate conditions (temperature, risks of avalanche, etc). For instance in the refuges on the main climbing routes to the

Mont-Blanc where Robach *et al.* [2016] conducted their study on drug intake in climbers, waking-up is scheduled at midnight or 01:00 am. Despite zolpidem has a short half-life (1.5-2.4 h) [Terzano *et al.* 2003], previous results indicate significant residual effects during early wakening at sea level with alterations in cognitive performances and car driving [Farkas *et al.* 2013; Danjou *et al.* 1999]. There is no data on the effects of zolpidem at early wakening during a high altitude stay where alpinists need full physical and cognitive capacities in order to reach safely their climbing goal. Based on previous studies having reported significant alterations in cognitive [Vermeeren *et al.* 2004; Farkas *et al.* 2013] and physical (e.g. impaired postural control [Boyle *et al.* 2009; Otmani *et al.* 2012) abilities some hours after zolpidem intake at sea level, the potential residual effects of zolpidem following early wakening at high altitude may represent a critical concern for climber safety.

The objective of this study was to assess the effects of zolpidem on i) cognitive function both at rest and during exercise and ii) postural control assessed following early waking-up at high altitude. We hypothesized that altitude exposure and zolpidem would alter cognitive function both at rest and during exercise and postural control measured 4 hours after drug intake.



# MATERIAL AND METHODS

---

## **Study design**

This is a randomized double-blind controlled cross-over study, registered under the number EudraCT 2015-004512-38 and having received ethical approval (CPP Sud Est V).

## **Subject selection**

Twenty-four healthy subjects (eight females) between 18 and 60 years-old were included. For each female subject, all sessions were scheduled at the same period of her menstrual period. All subjects resided at low altitude (<1,000 m of altitude) and were unacclimatized to high altitude at the time of the test (no sojourn above 2,000 m over the past two month). None was sedentary or highly trained (all subjects were physically active and engaged in a maximum of two endurance activity sessions per week).

Exclusion criteria were any somatic or psychiatric disease, hypnotics consumption, zolpidem intolerance, history of severe AMS, extreme circadian typology (assessed by Horne and Ostberg questionnaire [Horne *et al.* 1976], <30 or >70), insomnia or sleepiness (Epworth questionnaire >10 [Johns *et al.* 1991] or Pittsburg questionnaire >5 [Buysse *et al.* 1989]) and smoking.

## **Data collection**

### ***Protocol.***

After a familiarization session, subjects were evaluated on four occasions in Grenoble hospital (210 m) and at the Aiguille du Midi (at the top cable car station 3,800 m). Treatment oral administration was performed at 9:55 pm. After 3 hours and 30 minutes of sleep (at 1:30 am), subjects waked-up for blood sampling and to answer questionnaires. After a light standardized breakfast, postural evaluations were conducted. Then cognitive tests started at 2:00 am. The experimentations ended at 3:15 am.

### ***Cognitive tests.***

The cognitive tasks were performed by the participants seated on a cycle ergometer, equipped with two thumb response keys fixed on the top of the right and left handle grips, positioned in front of a screen located 1 m away. In each session, the participants performed three blocks of each cognitive task (the Simon cognitive test and the duration-production task, presented alternately and in a counterbalanced order), first at rest and then while cycling at 50% of their estimated maximal aerobic power at sea level (calculated based on the Wasserman formula [Beaver *et al.* 1986]) and at altitude (calculated as 80% of the normoxic maximal aerobic power basal on previous results [Fulco *et al.* 1998]). Heart rate and arteriolar oxygen saturation (SpO<sub>2</sub>) were continuously recorded (Nonin Onyx Oximeter, Plymouth, MN) during all cognitive test at rest and during exercise.

### *Simon cognitive test*

Simon cognitive test is a reaction time task where there is dimensional overlap between an irrelevant stimulus and the response [Simon *et al.* 1967]. The task included two equiprobable and randomized trial types: the congruent trials (response ipsilateral to the stimulus side), and the incongruent trials (response contralateral to the stimulus side). This conflict task permits to measure the Simon effect, additional time of response when there is an irrelevant stimulus (incongruent trials). That gives an approach of cognitive control. All the participants first performed a training phase during the familiarization session consisting of a minimum of 4 blocks of 64 trials. Two additional blocks were performed, if necessary, until the following learning criteria were achieved in one block: (a) intra-block reaction time variability below 25%; (b) inter-blocks reaction time variability with the previous block below 5%; (c) mean reaction time less than 400 ms; and (d) error rate between 3% and 10%.

During the experimental sessions, participants had to fixate on a white point, positioned in the center of the screen and they were required to respond, as quickly and accurately as possible, by pressing the appropriate response key according to the shape (i.e., square or circle) of a geometric symbol delivered either to the left or to the right of the fixation point. The distance from the fixation point to the stimulus located to either the right or left was 7.5 cm. Participants had to respond according to the shape of the stimulus while ignoring its spatial location. The stimulus-response mapping (for example, right response for a square and left response for a circle) was counterbalanced across participants. As soon as a response key was pressed or when a delay of 1.5 s after the stimulus on set had elapsed without a response, the stimulus was removed from the screen and the next trial began.

### *Duration-Production Task*

In a duration production task, the internal clock is evaluated with two factors: participants activation level and attention devoted to time. The duration-production task consists of pressing a button for a time interval learned during a training phase which was performed prior to each experimental session.

The training phase, largely inspired from protocols used in previous studies [Burle *et al.* 2001; Casini *et al.* 2013; Pomportes *et al.* 2017], consisted of two parts. For the first ten trials, a 600 Hz tone sounded for 1,100 ms. When the sound ended, a red circle appeared in the center of the screen indicating that participants could reproduce the duration of the sound by pressing the right button as long as the sound lasted. When the participants released the button, an auditory feedback was delivered. Five different feedbacks were used. If the produced interval was correct (less than 7.5% longer or shorter than the target), the feedback “correct” was delivered. If the produced duration was too long or too short (7.5–22.5% longer or shorter than the target), either the word “too long” or “too short” were delivered. If the duration was excessively long or short (more than 22.5% longer or shorter), the words “much too long” or “much too short” were delivered. After the first ten training trials, participants performed a second training block in which no additional model of target duration was delivered. During the remaining trials, once the red circle appeared on the screen, participants pressed the key for 1,100 ms. As in the ten first trials, an auditory feedback was delivered after each response. The participants continue until they produced 12 correct durations through 15 successive trials. A maximum of 50 trials was presented. If participants did not reach the criterion before the end of the block, they began a complete training phase again.

During the experimental sessions, participants were required to press the right button for 1,100 ms. The participants produced the duration once the red circle appeared on the

screen. Participants had to press the button as long as necessary to time the required duration (1,100 ms). No feedback on performance was given. One and a half seconds after the release of the key, the red circle appeared again, indicating that the next trial could be initiated.

### *Cerebral oxygenation*

Oxyhaemoglobin (HbO<sub>2</sub>) and deoxyhaemoglobin (HHb) concentration changes and tissue oxygenation index (TSI) were measured throughout cognitive tests over left prefrontal cortex site using a continuous wave near infra-red spectroscopy (NIRS) system (Portalite, Artinis Medical Systems, Einsteinweg, The Netherlands). Total haemoglobin concentration ([HbTot]) was calculated as the sum of [HHb] and [HbO<sub>2</sub>] and reflected the changes in tissue blood volume within illuminated area [Hoshi *et al.* 2001; Van Beekvelt *et al.* 2001]. The left prefrontal cortex NIRS signal was assessed between Fp1 and C3 according to the international 10-20 EEG system. The cortical probe was secured to the skin with double-sided tape and maintained with headband. Optode positioning was identical during all sessions.

### ***Postural evaluation.***

Standing postural control was assessed by analyzing the excursions of the center of pressure (CoP), using a posturographic platform (Feetest 6, Technoconcept, Mane, France) settled in a quiet dedicated room, one meter away from a clueless white wall. Subjects stood on the platform barefoot, their feet placed accorded to the AFP-85 norms [A.F.P. 1985] (4 cm inter-malleolus distance, with anterior open angle of 30°). To best reproduce the constraints faced by alpinists during climbing, subjects wore a 10 kg backpack. During the acquisitions, subjects were instructed to maintain a quiet and

stable erected posture, their arm hanging down freely along their body, and to stay still until the evaluator allowed them to move.

Evaluations were performed eyes opened (two trials, subjects were instructed to stare at the white wall) and then closed (two trials). Each trial lasted 30 s and trials were interspersed by a fixed 30-s period of rest. Data were recorded with a sampling rate of 40 Hz, and calculate using the Posturewin 4<sup>®</sup> software. As a measure of standing postural control performance, the amount of sway was evaluated by calculating CoP area (90% confidence ellipse, mm<sup>2</sup>). To accurately describe the postural control strategies, length (mm), standard deviation in antero-posterior plane (mm), speed (mm/s) and variance of speed of CoP were also calculated. Romberg Index was calculated (ratio between CoP area recorded eyes closed and CoP area recorded eyes opened) to assess the contribution of vision in the postural control strategy. As an information of energy expenditure required to maintain a stable balance, the length / area ratio (= CoP length / CoP area) was calculated [Gagey *et al.* 1999].

### ***Sleep recording.***

Sleep evaluation was performed with a polygraph (Vista O<sub>2</sub>-Novacore, Paris, France) recording nasal flow, thoracic movements, electrocardiogram and SpO<sub>2</sub>. Computerized data processing was controlled by one of the experimenter (SB) to obtain the apnea-hypopnea index (AHI) and the oxygen desaturation index (ODI) (3% SpO<sub>2</sub> drop during ≥10 s).

### ***Questionnaires.***

The Lake Louise Score (LLS) was used to evaluate symptoms of AMS by a self-assessment questionnaire (5 items scored between 0 and 3: headache, gastrointestinal disturbance, fatigue, dizziness and sleeping disorders) and a clinical evaluation (2 items scored between 0 and 4: ataxia, mental state and functional evaluation and 1 item scored between 0 and 2: peripheric edema) [Roach *et al.* 1993]. The 9-point Karolinska sleepiness scale [Akerstedt *et al.* 1990] was used to evaluate subjective sleepiness between grade 1 = very alert and grade 9 = very sleepy (fighting sleep). In addition, sleep latency was rated by the subject as follows: 1= <15min, 2= 15 to 30min, 3= 30 to 45min and 4= >45min. Sleep quality was also evaluated by the subject as follows: 1= superficial, 2= transitional and 3= deep.

### ***Blood sampling and analyses.***

Venous blood sampling was performed at 1:40 am to measure the concentration of zolpidem in serum. The tubes were immediately centrifuged at 2,500 rpm during 10 min at 4°C for extracting the serum by micro-pipetting. Serum samples were frozen until biological analysis. Serum zolpidem concentrations were semi-quantitatively evaluated by a reverse-phase liquid chromatography performed on a rapid resolution HPLC system (Agilent 1,200 series) equipped with a SupelcoAscentis<sup>®</sup> C18 column.

### **Main outcome**

The main outcomes of this study are reaction time and error rate during the Simon cognitive test.

## **Secondary outcomes**

Secondary outcomes are time perception (accuracy and variability), postural performances (area, length and speed of CoP, antero-posterior displacement, Romberg index and CoP length/area ratio), sleeping parameters (AHI, ODI, and average SpO<sub>2</sub>), symptoms (LLS and Karolinska sleepiness scale), sleeping quality (according to self-assessment questionnaire: sleep quality and latency) and NIRS parameters (TSI and haemoglobin concentration changes in the left prefrontal cortex).

## **Sample size calculation**

Power assessment for the primary outcome (Simon test) was based on a minimum expected difference of 10% between zolpidem and placebo, similar to the effect of sleep deprivation previously evaluated by our group [Temesi *et al.* 2013]. Assuming an  $\alpha$  level of 5% and power of 80%, 24 subjects were required.

## **Statistical analysis**

Normality of distribution and homogeneity of variances of the main variables were confirmed using a Shapiro-Wilk normality test and the Levene's test, respectively. Two-way ANOVA (altitude  $\times$  treatment) with repeated measures were performed for each dependent variable. Post-hoc Tukey's tests were applied to determine a difference between two mean values if the ANOVA revealed a significant main effect or interaction effect. For all statistical analyses, a two-tailed alpha level of 0.05 was used as the cut-off for significance. All statistical procedures were performed on Statistica version 10 (Statsoft, Tulsa, OK). All data are expressed as means  $\pm$  standard deviation (SD).



# RESULTS

---

Twenty-four subjects were included in this study and the protocol was complete for twenty-two subjects between June and November 2016. Two subjects withdraw during the study due to lack of time to complete all the experiments.

## **Simon cognitive test**

Altitude exposure had no significant effect on the reaction time and the error rate (all  $p > 0.05$ ) but increased the Simon effect because the reaction time in incongruent trials only was lengthened (interaction altitude  $\times$  congruency,  $F = 8.31$ ,  $p < 0.01$ ; Figure 1).

Zolpidem lengthened reaction time both at sea level and at altitude (main treatment effect,  $F = 18.55$ ,  $p < 0.001$ ; interaction treatment  $\times$  altitude,  $F = 0.39$ ,  $p = 0.54$ ), but the effect was smaller during exercise (interaction treatment  $\times$  exercise,  $F = 5.42$ ,  $p = 0.03$ ; Figure 1 A and B). At altitude at rest, the Simon effect tended to be more pronounced with zolpidem (zolpidem  $36.6 \pm 4.15$ s vs placebo  $31.9 \pm 2.94$ s) because the effect of zolpidem was greater in incongruent trials (interaction congruency  $\times$  treatment,  $F = 3.82$ ,  $p = 0.06$ ; Figure 1 A and B). Zolpidem did not affect the Simon effect at sea level and during exercise (results not shown, all  $p > 0.05$ ).

Zolpidem increased error rate in incongruent trials while error rate in congruent trials was unchanged compared to placebo (interaction treatment  $\times$  congruency,  $F = 6.82$ ,  $p = 0.02$ ; Figure 1 C and D). These effects were similar at sea level and at altitude (interaction treatment  $\times$  altitude,  $F = 0.97$ ,  $p = 0.34$ ) and at rest and during exercise (interaction treatment  $\times$  exercise,  $F = 0.13$ ,  $p = 0.72$ ).

### **Duration-production task**

Durations tended to be longer at altitude compared to sea level (main effect of altitude,  $F=3.21$ ,  $p=0.08$ ) and temporal variability was significantly increased by altitude (main effect of altitude,  $F=8.94$ ,  $p<0.01$ ; Figure 2).

No effect of treatment was observed regarding produced temporal durations (main treatment effect,  $F=0.51$ ,  $p=0.48$ ), both at sea level and at altitude (interaction treatment  $\times$  altitude,  $F=0.97$ ,  $p=0.34$ ), at rest and during exercise (interaction treatment  $\times$  exercise,  $F=0.13$ ,  $p=0.72$ ; Figure 2 A and B).

Temporal variability was increased by zolpidem (main effect of treatment,  $F=14.10$ ,  $p=0.001$ ; Figure 2 C and D). Zolpidem tended to increase temporal variability to a greater extent than placebo at altitude (interaction treatment  $\times$  altitude,  $F=3.45$ ,  $p=0.07$ ).

### **SpO<sub>2</sub>, heart rate and NIRS data during cognitive tests**

Altitude decreased SpO<sub>2</sub> and increased heart rate both at rest and during exercise (all  $p<0.05$ ; Supplemental material, Table S1). At rest, altitude had no significant effect on TSI. During exercise, TSI decreased less at altitude than at sea level during the cognitive tests (main altitude effect,  $F=11.85$ ,  $p=0.002$  and  $F=11.68$ ,  $p=0.003$  during Simon cognitive test and duration production task respectively; Figure 3). At altitude, the increase in [HbO<sub>2</sub>] during the cognitive tasks was larger at rest and lower during exercise, compared to sea level (Table S1). At altitude, the reduction in [HHb] during the cognitive tasks was smaller compared to sea level at rest only (Table S1). At altitude, the increase in [HbTot] during the cognitive tasks was larger at rest and lower during exercise (Table S1).

Zolpidem had no effect on SpO<sub>2</sub> but increased mean heart rate at rest (main treatment effect, F=36.85, p<0.001) and during exercise (main treatment effect, F=4.46, p=0.04; Table S1).

The increase in TSI during the cognitive tasks at rest was larger with zolpidem compared to placebo (main treatment effect, F=5.60; p=0.03 and F=5.93; p=0.02 during Simon cognitive test and duration-production task, respectively; Figure 3 A and C). During exercise, zolpidem has no significant effect on TSI changes during the Simon cognitive test (main treatment effect, F=1.31, p=0.27) and the duration-production task (main treatment effect, F=1.74, p=0.20; Figure 3 B and D).

Zolpidem had no effect on [HbO<sub>2</sub>], [HHb], [HbTot] changes during the cognitive tests. (Supplemental material, Table S1).

### **Postural evaluation**

Altitude increased the CoP length/area ratio (mean of the two nights 2.2±1.0) compared to sea level (mean of the two nights 1.9±0.9) but had no effect on the other postural variables (Table 1).

Zolpidem increased CoP area compared to placebo (mean of the two nights with zolpidem 236.1±169.8 mm<sup>2</sup> vs mean of the two nights with placebo 119.6±59.3 mm<sup>2</sup>; Table 1). The variation of CoP displacement in antero-posterior plane was increased by zolpidem compared to placebo (mean of the two nights with zolpidem 4.45±2.15 mm vs mean of the two nights with placebo 3.35±1.15 mm; Table 1). Zolpidem decreased the CoP length/area ratio (mean of the two nights 1.65±1.1) compared to placebo (mean of the two nights 2.4±0.75; Table 1). There was no interaction between altitude and treatment (all p>0.05). Romberg index was not modified by zolpidem (Table 1).

### **Sleep recordings and questionnaires**

Altitude increased significantly AHI (mean of the two nights at altitude  $24.8 \pm 32.0$  event/h vs mean of the two nights at sea level  $6.9 \pm 5.2$  event/h at sea level) and ODI (mean of the two nights at altitude  $39.7 \pm 31.8$  event/h vs mean of the two nights at sea level  $3.7 \pm 4.8$  event/h; Table 2). Altitude decreased significantly mean SpO<sub>2</sub> (mean of the two nights at altitude  $77.6 \pm 3.9\%$  vs mean of the two nights at sea level  $92.8 \pm 9.3\%$ ) and sleep quality (mean of the two nights at altitude  $2.1 \pm 0.8$  vs mean of the two nights at sea level  $2.4 \pm 0.6$ ; Table 2). Significant altitude effects were also observed on LLS, ataxia and functional evaluation (Table 2).

There was no effect of zolpidem on AHI, mean SpO<sub>2</sub> and minimal SpO<sub>2</sub> while with zolpidem ODI increased significantly less at altitude (Table 2). Compared to placebo, zolpidem increased significantly sleep quality and decreased sleeping latency (Table 2). Regarding symptoms, zolpidem compared to placebo increased significantly LLS, sleepiness, dizziness, ataxia and functional evaluation (Table 2).

### **Blood sampling**

Mean zolpidem concentration was  $56.3 \pm 29.2$  ng/ml at altitude (14 subjects had a concentration  $>50$  ng/ml) and  $47.6 \pm 26.5$  ng/ml at sea level (9 subjects had a concentration  $>50$  ng/ml). Zolpidem concentration did not differ at sea level and at altitude ( $p=0.27$ ). Zolpidem was not identified in any serum sample following placebo intake.

# DISCUSSION

---

The results indicate that at early morning 4 h following zolpidem intake, the reaction time and error rate are increased during the Simon cognitive test as well as the temporal variability during the duration-production task. Compared to placebo, zolpidem altered several parameters of postural control such as the CoP area and antero-posterior displacement. Zolpidem improved sleep quality but increased symptoms of AMS, dizziness and ataxia. Altogether, these results indicate that zolpidem intake and early waking-up are associated with significant alterations in cognitive and postural performances and increased symptoms.

## **Cognitive performances**

In the present study, we investigated executive functions which refer to a set of processes allowing for a flexible behavior adapted to an ever-changing environment. More specifically, we focused on cognitive control and time estimation, continuously involved in any goal-oriented behavior by using two well-established and widely used cognitive tasks, respectively a Simon task and a duration-production task. Reaction times during the Simon cognitive test were shorter during exercise, and the exercise facilitator effect was stronger with subjects under zolpidem (in a sub-optimal state). This suggests that physical exercise and zolpidem probably act on a common process, but in an opposite way. According to Temesi *et al.* [2013], exercise limits the impact of sleep deprivation on cognition, thus explaining why the adverse effects of zolpidem are more visible at rest than during an effort.

Also, an interaction between zolpidem and congruence was found, with longer reaction time and a higher number of errors in incongruent trials, showing that the interference (or Simon effect) was stronger under zolpidem. This result might suggest that the cognitive control is less effective under zolpidem, hence explaining why the inhibition of non-pertinent responses during the Simon task was less efficient.

Zolpidem has no significant effect on temporal production during the duration-production task, but temporal precision was subject to a significant altitude and a significant exercise main effect, without an interaction between the two factors. The lack of interaction suggests that the two factors have an effect on different processes of the internal clock. As seen in the literature [Burle *et al.* 2011], exercise has an effect on the pacemaker activation speed, therefore suggesting that altitude has an effect on the pacemaker accumulation process. The effect on the attention/concentration capacity might be explained by a slower accumulation of the signals, which is coherent with over-production shown in our results.

The temporal variability was affected by both altitude and zolpidem. The non-significant interaction between the two factors ( $p=0.07$ ) may reveal that the variability was increased by zolpidem to a larger extent at high altitude. This result suggests that zolpidem and altitude may both interact on the same attention accumulation process, presumably modifying the focal attention.

Cerebral oxygenation was measured during the cognitive test in order to provide some information about the mechanisms associated with the effects of zolpidem on cognitive performances. The TSI only was affected by zolpidem during both cognitive tasks at rest, with larger increase in response to the cognitive tasks with zolpidem. We can hypothesize that in order to compensate the treatment adverse effects, the prefrontal cortex increases its level of activation (as shown by larger increase in oxygenation)

during the cognitive tasks. The lack of zolpidem effect on the TSI during exercise might suggest that its facilitator effect makes the increase in prefrontal cortex activation observed at rest unnecessary during the cognitive tasks performed while exercising.

It should be emphasized that the effects of zolpidem on cognitive performances could be explained by cerebral mechanisms involving other areas than the prefrontal cortex which was the only region investigated under the present experimental conditions. Licata *et al.* [2013] have demonstrated with BOLD fMRI that zolpidem does not alter the prefrontal cortex oxygenation at rest. Also, many studies have established that exercise influences cerebral blood flow with neurotransmitters such as dopamine, norepinephrine, serotonin and cortisol, thus modifying cognitive functions [Brisswalter *et al.* 2002; McMorris *et al.* 2011]. This might be the case in our study during the cognitive tasks at sea level, with a large increase in [HbO<sub>2</sub>], an improvement in both the Simon's task mean reaction time and the time estimation during the duration-production task. However, at high altitude, our results show the opposite effect, with a decrease in [HbO<sub>2</sub>], and [HbTot], while still having an improvement of the cognitive functions with exercise. This could be explained by a prefrontal cortex hypoperfusion in response to hypocapnia induced by some hyperventilation secondary to hypoxemia aggravated by the exercise. Nonetheless we cannot rule out that the gain in cognitive functions during exercise could be linked to changes in brain oxygenation in areas that we did not monitor.

## **Postural evaluation**

Average speed is an important postural criterion as it is the most effective postural central control indicator, especially concerning the neuromuscular control [Palmieri *et al.* 2002]. Average speed is the most informative criterion as it normalizes length in relation to time, thereby monitoring the average dynamic of the CoP linear shifting. The area is usually used as another relevant criterion as it is the most representative and shows a good sensitivity, but it assesses the sway postural system strategy (postural oscillation control precision) whereas the speed is a dynamic criterion [Weber *et al.* 2010].

Our force platform measures have highlighted a zolpidem adverse effect on descriptive postural parameters such as the CoP displacement area and the antero-posterior standard deviation of the CoP shifting length. These results are in accordance with the literature regarding the zolpidem effects on postural control at sea level [Nakamura *et al.* 2004; Boyle *et al.* 2009; Otmani *et al.* 2012] and underline the significant impact of the treatment on posture. The Romberg index (closed eyes/open eyes area ratio) did not show a pathological value ( $1 < RI < 2.5$ ), therefore suggesting that our subjects presented a weak visual dependency. This underlines the integrity at altitude of compensatory mechanisms carried out at the central level based on the other sensorial entries involved in the central control.

The CoP ratio (=length/area) correspond to the length traveled by the center of pressure by surface unit and represents energy dispensed to maintain posture. In our study, we have observed a decreased ratio under zolpidem. Although the CoP area was increased, the unstable subject under zolpidem may not increase his energetic expenditure in order to control his orthostatic posture. He either may not realize that he is unbalanced, or the tactical postural strategy is failing [Gagey *et al.* 2004]. In contrast to other studies, we



did not find any significant effect of altitude exposure [Wagner *et al.* 2011; Stadelmann *et al.* 2015]. This could be explained by some differences in our experimental protocol compared to previous studies. Our subjects were bare foot on the force platform, which enhances the proprioceptive feed-back and thus the stability, compared to shod subjects. The type of shoes seems to significantly modify the ankle external stabilization conditions [Bruyneel *et al.* 2014] as it changes the tridimensional foot support.

### **Sleep and symptoms**

Our results show that a zolpidem intake before sleeping increases significantly vertigo and ataxia in association with a deterioration of objective functional estimation while wakening at 01:30 am. Our data are in accordance with the literature regarding balance alteration and augmented falling risks after a zolpidem intake [Allain *et al.* 2005; Frey *et al.* 2011]. However, we have not found any clinical alteration at 07:00 am (only the altitude effect persisted, results not shown). We assume that zolpidem's short acting pharmacokinetic characteristics might explain the lack of adverse effects (at least based on self-reported symptoms and clinical evaluation) later in the morning.

Our results regarding polygraphy recordings, such the increase in the AHI, the increase of desaturations and the decrease in the average oxygen saturation level observed at altitude are in accordance with the literature on the effects of high altitude on sleep. Similar to the results of Beaumont *et al.* [2007], there was no impact of zolpidem on AHI at altitude.

The decrease in ODI under zolpidem at high altitude may suggest that this medication affects the hypoxemic consequences of nocturnal respiratory perturbations secondary to high altitude exposure. A reduction in the number of hypoxia-reoxygenation events following zolpidem intake could diminish the physiological stress caused by sleep at

high altitude. The reason why this index of desaturation is improved by zolpidem without any changes on the hypopnea-apnea index, nor on the nocturnal saturation average, has yet to be explained.

Following zolpidem intake, the subjects reported an improved sleep quality with a diminished sleeping latency, allowing to overcome at least in part the negative effects of high altitude on sleep. The analysis of the Karolinska score has shown that the capacity to stay awake 4 hours after the zolpidem consumption is significantly deteriorated. This effect is critical concerning the use of this drug during sojourn at high altitude with climbing activities, with potential deleterious consequences on the safety of climbers using zolpidem.

### **Blood sampling**

Although zolpidem has a rapid elimination rate, in almost 60% of the blood sample zolpidem concentration was  $>50\text{ng/ml}$  4 h after drug intake. This concentration is known to induce cognitive alterations [Farkas *et al.* 2013] and the Food Drug and Administration had published in 2015 recommendations [FDA 2015] to reduce this risk to have a concentration  $>50\text{ng/ml}$  at wakening.

# CONCLUSION

---

This randomized controlled and double-blind study demonstrates objectively the residual effects of zolpidem intake at altitude with an early waking-up as commonly done by alpinists. The cognitive performances were altered with increased reaction time, error rate and temporal estimation variability, indicating substantial functional impairments. Several parameters of postural control were also altered, such as the CoP area and the antero-posterior displacement, emphasizing objective physical alterations. As expected zolpidem improved sleep quality and reduced sleep latency but it also increased symptoms of AMS, dizziness and ataxia and altered functional evaluation. Altogether, these results indicate that zolpidem intake and early waking-up are associated with significant alteration in cognitive and postural performances and increased symptoms which may be deleterious for alpinists safety and climbing abilities.

TITRE : Effets d'une prise unique de 10mg de zolpidem en haute altitude (3800m) sur les performances cognitives et posturales : Essai randomisé contrôlé contre placebo en *cross-over* et double aveugle.

## CONCLUSION

**Introduction** : Le sommeil est perturbé en haute altitude (dès 3500m, notamment par altération du contrôle respiratoire en hypoxie hypobarique), motivant les alpinistes à consommer des hypnotiques (ex. le zolpidem) pour améliorer leur récupération avant la course du lendemain. Aucune étude n'a à ce jour étudié les éventuels effets résiduels d'une telle prise médicamenteuse lors d'un lever nocturne (comme c'est le cas pour la pratique de l'alpinisme en haute montagne).

L'objectif de notre travail a été d'évaluer si une telle prise médicamenteuse au coucher pouvait être responsable d'une altération des capacités cognitives et posturales au réveil des alpinistes en pleine nuit (environ 4 heures après la prise).

**Méthode** : Les tests cognitifs ont consisté en une tâche de Simon et une tâche de production temporelle, au repos et à l'exercice, avec enregistrement simultané de l'oxygénation cérébrale, au réveil d'une nuit de trois heures trente (avec enregistrement polygraphique) sous zolpidem (10mg) versus placebo, en *cross-over* et double aveugle.

Sur le plan postural, des enregistrements sur plateforme de force (yeux ouverts et fermés avec un sac de 10kg sur le dos) ont été réalisés. La présence de symptômes de mal aigu des montagnes, la qualité du sommeil (score de 1 à 3) et de l'éveil ont également été évalués par questionnaire.

**Résultats** : 22 sujets ont été évalués lors de 2 nuits en plaine (Grenoble, 210m) et 2 nuits en altitude (Aiguille du midi, 3800m) entre juin et novembre 2016.

Les résultats ont mis en évidence une augmentation du temps de réaction sous zolpidem ( $407 \pm 9$ ms vs  $380 \pm 11$ ms sous placebo ;  $p < 0,001$ ) associée à une modification de l'oxygénation tissulaire cérébrale, ainsi qu'une augmentation de l'effet Simon significative en altitude ( $p < 0,01$ ) et tendancielle sous traitement ( $p = 0,06$ ). Le taux d'erreurs sur les essais incongruents a été plus important sous zolpidem que sous placebo ( $10 \pm 1\%$  vs  $8 \pm 1\%$  ;  $p < 0,01$ ). Le zolpidem pris en altitude a augmenté la

variabilité temporelle par rapport au placebo ( $p < 0,001$ ). Un effet délétère du zolpidem a été montré sur les paramètres posturaux descriptifs tels que la surface de déplacement du centre de pression ( $236 \pm 172 \text{ mm}^2$  sous zolpidem vs  $120 \pm 59 \text{ mm}^2$  sous placebo ;  $p < 0,001$ ) et l'écart-type avant-arrière de la longueur de déplacement du centre de pression ( $4,5 \pm 2,2 \text{ mm}$  vs  $3,3 \pm 1,2 \text{ mm}$  ;  $p = 0,002$ ) sans effet surajouté de l'altitude. Les vertiges et l'ataxie en ont été la traduction clinique (vertiges :  $0,57 \pm 0,8$  vs  $0,16 \pm 0,4$  sous placebo ;  $p = 0,003$  ; ataxie :  $0,68 \pm 0,7$  vs  $0,23 \pm 0,4$  sous placebo ;  $p = 0,004$ ).

Il n'y a pas eu d'altération des principaux paramètres polygraphiques (IAH et  $\text{SpO}_2$  moyenne non modifiés) et le sommeil a été de meilleure qualité ( $2,6 \pm 0,6$  vs  $1,9 \pm 0,8$  sur questionnaires ;  $p < 0,001$ ) sous zolpidem en altitude.

**Conclusion** : Une prise de 10mg de zolpidem au coucher en haute altitude a été responsable d'une altération des performances cognitives et du contrôle postural au réveil en pleine nuit sans effet sur la ventilation pendant le sommeil.

VU ET PERMIS D'IMPRIMER  
Grenoble, le 07/11/17

LE DOYEN

  
Pr. J. P. ROMANET  
Pour le Président  
et par délégation  
Le Doyen de Médecine  
Pr. Jean-Paul ROMANET

LE PRESIDENT DE LA THESE

Pr J-F. PAYEN DE LA GARANDERIE



# BIBLIOGRAPHIE :

---

- A.F.P. Normes 1985. Editées par l'ADAP (Association pour le Développement et l'Application de la Posturologie) 20 rue du rendez-vous, 75012 Paris.
- Ainslie P.N., Lucas S.J.E., Burgess KR. Breathing and sleep at high altitude: review. *Respir Physiol Neurobiol* 2013;188(3):233-56
- Akerstedt T., Gillberg M. Subjective and objective sleepiness in the active individual. *Int J Neurosci* 1990 May;52(1-2):29-37
- Allain H., Bentué-Ferrer D., Polard E., Akwa Y., Patat A. Postural instability and consequent falls and hip fractures associated with use of hypnotics in the elderly: a comparative review. *Drugs and aging* 2005;22(9):749-65
- Anholm, J.D., Powles, A.C., Downey, R., Houston, C.S., Sutton, J.R., Bonnet, M.H. and Cymerman, A. Operation Everest II: arterial oxygen saturation and sleep at extreme simulated altitude. *Am Rev Respir Dis* 1992;145(4pt1):817-26
- Beaumont M., Batéjat D., Coste O., Van Beers P., Colas A., Clère J.M., et al. Effects of Zolpidem and zaleplon on sleep, respiratory patterns and performance at a simulated altitude of 4,000m. *Neuropsychobiology* 2004;49(3):154-62
- Beaumont M., Batéjat D., Piérard C., Van Beers P., Philippe M., Léger D., et al. Zaleplon and Zolpidem objectively alleviate sleep disturbances in mountaineers at a 3,613 meter altitude. *Sleep* 2007 Nov;30(11):1527-33
- Beaumont M., Goldenberg F., Lejeune D., Marotte H., Harf A. and Lofaso F. Effect of zolpidem on sleep and ventilatory patterns at simulated altitude of 4,000 meters. *American journal of respiratory and critical care medicine* 1996;153(6):1864-1869
- Beaver W.L., Wasserman K., Whipp B.J. A new method for detecting anaerobic threshold by gas exchange. *Journal of Applied Physiology* 1986;60:2020-27
- Boyle J., Danjou P., Alexander R., Calder N., Gargano C., Agrawal N., Fu I., McCrea J.B., Murphy M.G. Tolerability, pharmacokinetics and night-time effects on postural sway and critical flicker fusion of glabaxadol and zolpidem in elderly subjects. *Br J Clin Pharmacol* 2009 Feb;67(2):180-90
- Brisswalter J., Collardeau M., René A. Effects of acute physical exercise characteristics on cognitive performance. *Sports medicine* 2002;32(9):555-66
- Bruyneel A.V., Humbert A., Bertrand M. Influence de l'altitude sur les stratégies d'équilibre pour les alpinistes: effet de l'âge et de l'expertise. *Kinesitherscient* 2014;55

- Burle B. and Casini L. Dissociation between activation and attention effects in time estimation: implications for internal clock models. *Journal of Experimental Psychology: Human Perception and Performance* 2001;27(1):195
- Buysse D.J., Reynolds C.F., Monk T.H., Berman S.R., Kupfer D.J. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989 May;28(2):193-213
- Casini L., Beauvir C., Burle B. and Vidal F. How does one night of sleep deprivation affect the internal clock ? *Neuropsychologia* 2013;51(2):275-283
- Casini L., Vidal F. The SMAs: neural substrate of the temporal accumulator? *Frontiers in integrative neuroscience* 2011.5:35
- Danjou P., Paty I., Fruncillo R., Worthington P., Unruh M., Cevallos W., et al. A comparison of the residual effects of zaleplon and zolpidem following administration 5 to 2 h before awakening. *Br J Clin Pharmacol* 1999 Sep;48(3):367-74
- Farkas R.H., Unger E.F., Temple R. Zolpidem and Driving Impairment - Identifying Persons at Risk. *N Engl J Med* 2013 Aug 22;369(8):689-91
- FDA 2015 : Research C for DE and. Drug Safety and Availability - FDA Drug Safety Communication: Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist)
- Frey J.D., Ortega J.D., Wiseman C., Farley C.T., Wright K.P. Influence of zolpidem and sleep inertia on balance and cognition during nighttime awakening: a randomized placebo-controlled trial. *J Am Geriatr So* 2011. 59:73-81
- Fulco C.S., Rock P.B., Cymerman A. Maximal and submaximal exercise performance at altitude. *Aviat Space Environ Med* 1998 Aug;69(8):793-801
- Gagey G, Weber B. Posturologie, régulation et dérèglement de la station debout. Paris: Masson, 1999.
- Gagey P.M., Weber B., Posturologie : régulation et dérèglement de la station debout, Version 3; Paris: Masson 2004
- Hackett PH, Roach RC. High-altitude illness. *N Engl J Med* 2001 Jul 12;345(2):107-14
- Horne J.A., Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol* 1976;4(2):97-110
- Hoshi Y., Kobayashi N. and Tamura M. Interpretation of near-infrared spectroscopy signals: a study with a newly developed perfused rat brain model. *J Appl Physiol* 2001;90:1657-1662
- Johns M.W. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991 Dec;14(6):540-5

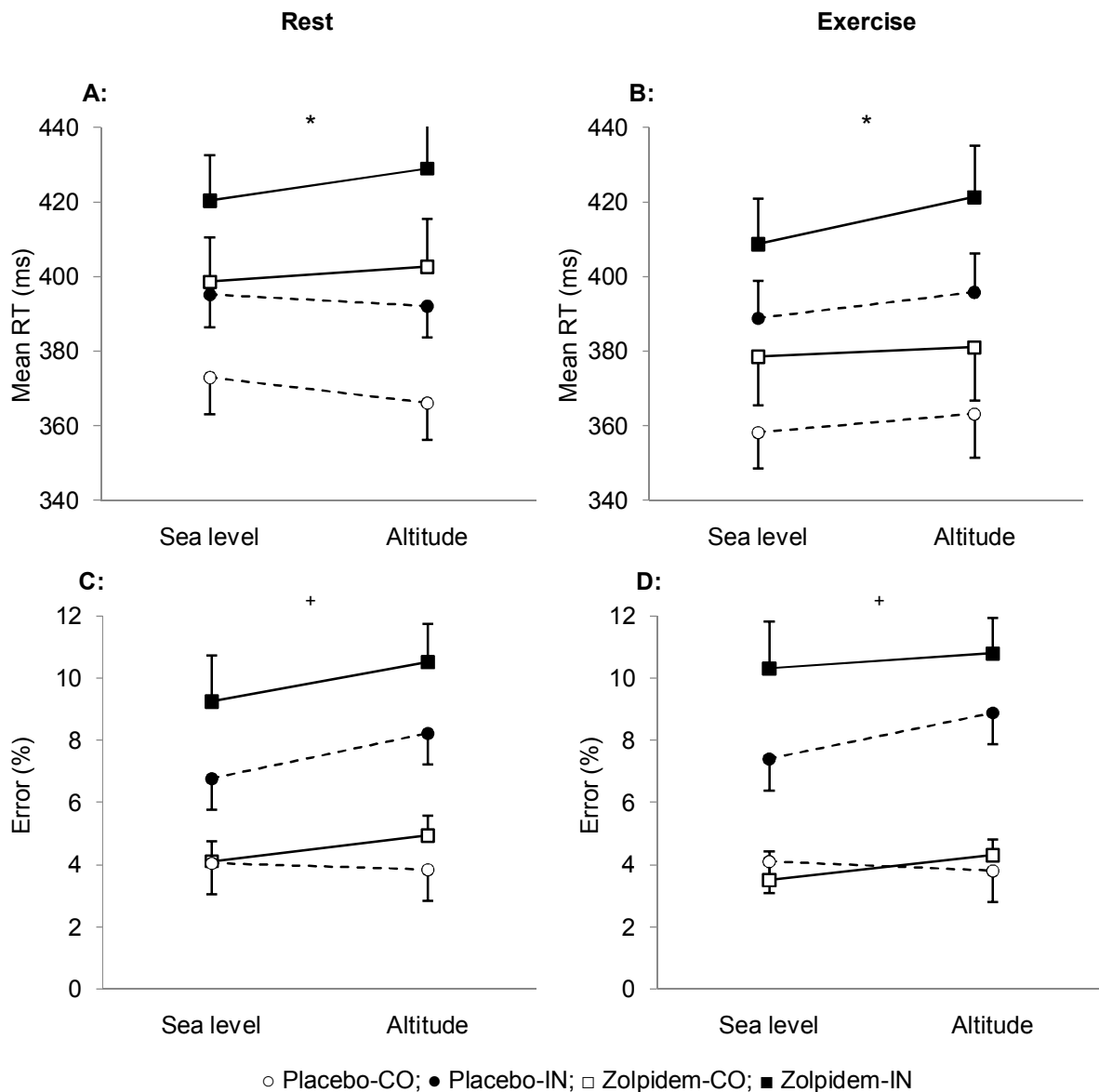
- Johnson, P.L., Edwards, N., Burgess, K.R. and Sullivan, C.E. Sleep architecture changes during a trek from 1400 to 5000 m in the Nepal Himalaya. *Journal of sleep research* 2010;19(1p2):148-156
- Jouanin J, Dussault C, Van Beers P, Piérard C, Beaumont M. Short half-life hypnotics preserve physical fitness and altitude tolerance during military mountainous training. *Mil Med* 2009 Sep;174(9):964-70
- Katzung BG. Pharmacologie fondamentale et clinique. Padoue, Italie: Piccin; 2006:1669
- Lake Louise consensus AMS score 1991
- Licata S.C., Nickerson L.D., Lowen S.B., Trksak G.H., MacLean R.R., Lukas S.E. The hypnotic zolpidem increases the synchrony of BOLD signal fluctuations in widespread brain networks during a resting paradigm. *NeuroImage* 2013;70:211-22
- McMorris T., Hale B.J., Barwood M., Costello J., Corbett J. Effect of acute hypoxia on cognition: A systematic review and meta-regression analysis. *Neuroscience & Biobehavioral Reviews* 2017
- Nakamura M., Ishii M., Niwa Y., Yamazaki M., Ito H. Temporal changes in Postural Sway Caused by Ultrashort-Acting Hypnotics: Triazolam and Zolpidem. *ORL* 2005;67:106-12
- Palmieri R.M., Ingersoll C.D., Stone M.B., Krause B.A. Center-of-pressure parameters used in the assessment of postural control. *J sport rehabil* 2002;11:51-66
- Pomportes L, Brisswalter J, Casini L, Hays A, Davranche K. Cognitive Performance Enhancement Induced by Caffeine, Carbohydrate and Guarana Mouth Rinsing during Submaximal Exercise. *Nutrients* 2017;9(6):589
- Otmani S., Metzger D., Guichard N., Danjou P., Nir T., Zisapel N., Katz A. Effects of prolonged-release melatonin and zolpidem on postural stability in older adults. *Hum Psychopharmacol clin exp* 2012 May;27(3):5268-71
- Roach R., Hackett P. Lake Louise consensus on definition, and quantification of altitude illness. 1993
- Robach P., Trebes G., Lasne F., Buisson C., Méchin N., Botré F., Bouzat P. Drug Use on Mont Blanc : A study using automated urine collection. *PlosONE* 2016;11(6):e0156786
- Simon H.A., Motivational and emotional controls of cognition. *Psychological Review* 1967;74(1):29
- Stadelmann K., Latshang T.D., Lo Cascio C.M., Clark R.A., Huber R., Kohler M., Achermann P., Bloch K.E. Impaired postural control in healthy men at moderate altitude (160m and 2,590m): data from a randomized trial. *Plos ONE* 2015;10(2):e0116695



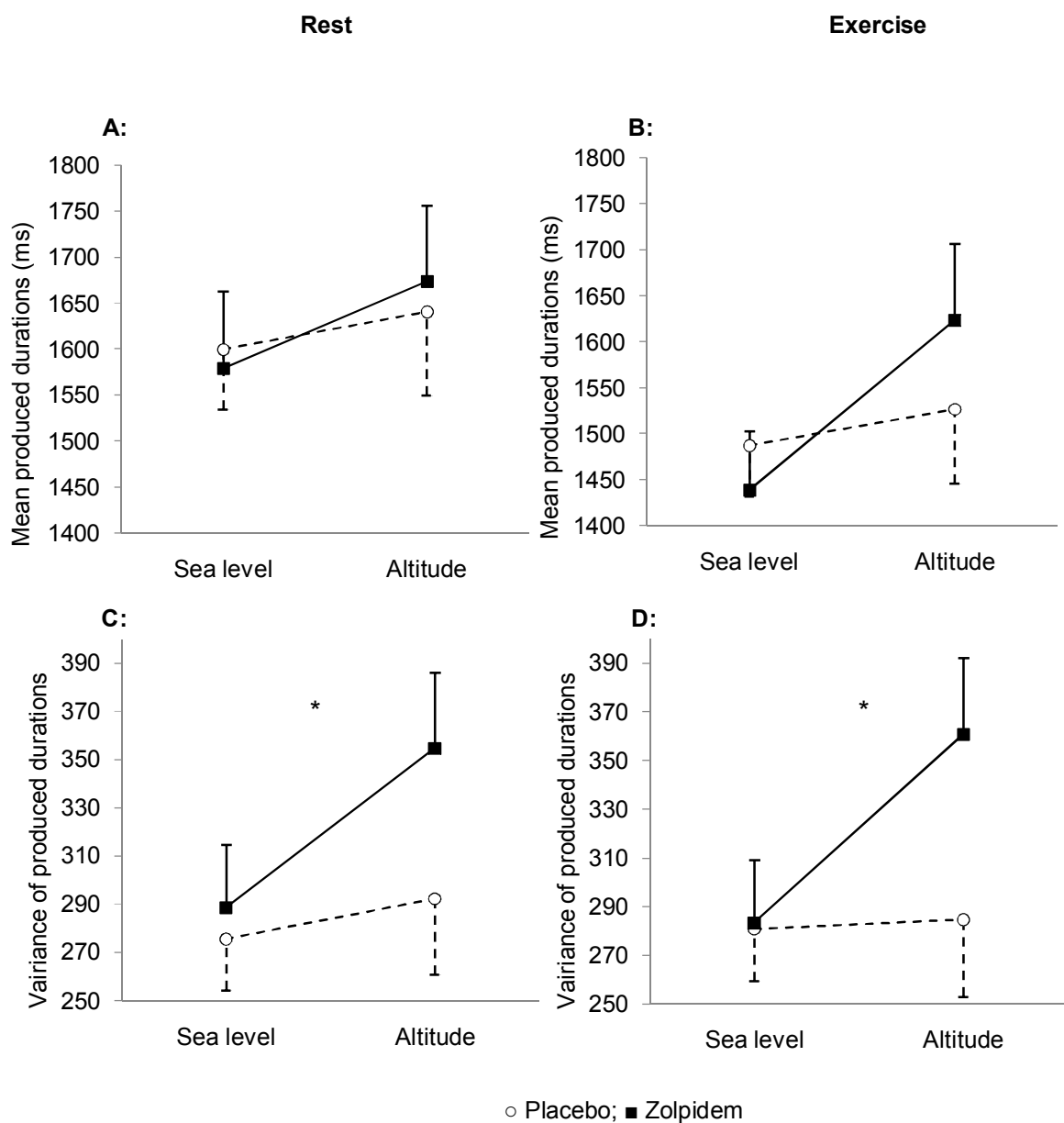
- Temesi J., Arnal P.J., Davranche K., Bonnefoy R., Levy P., Verges S., et al. Does central fatigue explain reduced cycling after complete sleep deprivation? *Med Sci Sports Exerc* 2013 Dec;45(12):2243-53
- Terzano M.G., Rossi M., Palomba V., Smerieri A., Parrino L. New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zapeplon. *Drug Saf* 2003;26(4):261-82
- Van Beekvelt M.C., Colier W.N., Wevers R.A. and Van Engelen B.G. Performance of near-infrared spectroscopy in measuring local O<sub>2</sub> consumption and blood flow in skeletal muscle. *J Appl Physiol* 2001;90:511-519
- Vermeeren A. Residual effects of hypnotics: epidemiology and clinical implications. *CNS Drugs* 2004;18(5):297-328
- Wagner L.S., Oakley S.R., Vang P., Noble B.N., Cevette M.J., Stepanek J.P. Hypoxia-induced changes in standing balance. *Aviat Space Environ Med* 2011;82:518-22
- Weber B., Villeneuve P. Posturologie clinique : tonus, postures, attitudes. Paris: Masson 2010
- Windsor, J.S. and Rodway, G.W. Sleep disturbance at altitude. *Current opinion in pulmonary medicine* 2012;18(6):554-560

# ANNEXES

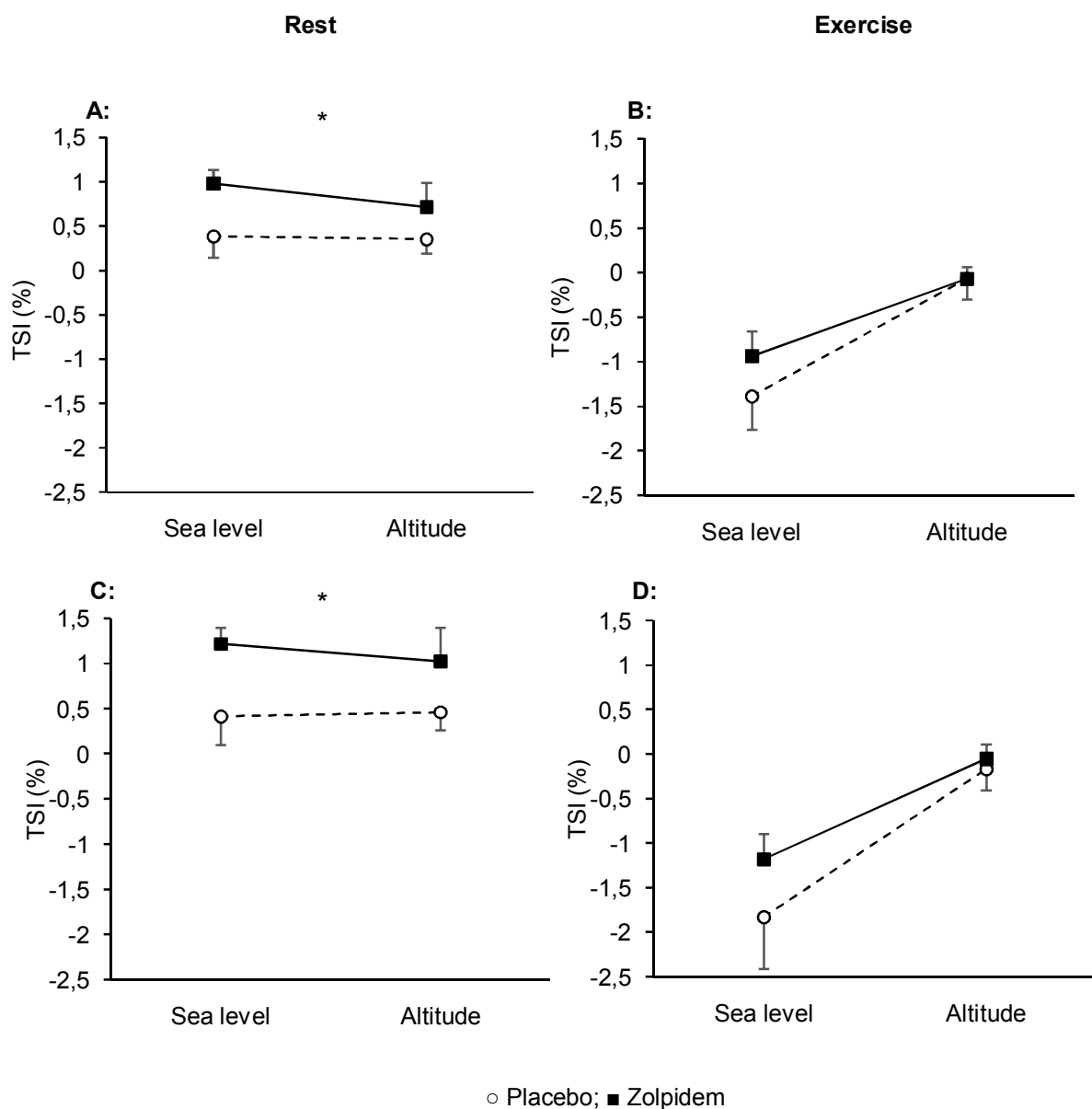
**Figure 1.** Simon task outcomes measured at rest and during exercise, at sea level and at altitude, following zolpidem or placebo administration. Panel A, reaction time (RT) at rest; Panel B, RT during exercise; Panel C, Error rate at rest; Panel D, Error rate during exercise. CO, congruent trials; IN, incongruent trials. Errors bars represent standard errors of mean. \* Main effect of treatment ( $p < 0.05$ ), + Effect of treatment in incongruent trials ( $p < 0.05$ ).



**Figure 2.** Duration-production task outcomes measured at rest and during exercise, at sea level and at altitude, following zolpidem or placebo administration. Panel A, time duration estimation at rest; Panel B, time duration estimation during exercise; Panel C, variability of time duration estimation at rest; Panel D, variability of time duration estimation during exercise. Errors bars represent standard errors of mean. \* Main effect of treatment ( $p < 0.05$ ).



**Figure 3.** Prefrontal cortex oxygenation (Tissue saturation index, TSI) measured by near infrared spectroscopy during the cognitive tasks at rest and during exercise, at sea level and at altitude, following zolpidem or placebo administration. Panel A, TSI during Simon test at rest; Panel B, TSI during Simon test during exercise; Panel C, TSI during time estimation at rest; Panel D, TSI during time estimation during exercise. Errors bars represent standard errors of mean. \* Main effect of treatment ( $p < 0.05$ ).



**Table 1.** Displacement of the center of pressure (CoP) during the postural evaluation with eyes opened at sea level and at altitude, following zolpidem or placebo administration.

	Sea level Placebo	Sea level Zolpidem	Altitude Placebo	Altitude Zolpidem	Main treatment effect	Main altitude effect	Interaction altitude x treatment
<b>CoP area</b> (mm <sup>2</sup> )	126.5 ±61.0	240.4 ±134.4	112.7 ±57.5	231.7 ±205.2	F(1,21)=22.4 2 p<0.001	F(1,21)=0.36 p=0.556	F(1,21)=0.02 p=0.905
<b>Length</b> (mm)	247.5 ±74.0	262.6 ±70.6	264.3 ±74.8	267.8 ±98.1	F(1,21)=0.69 p=0.416	F(1,21)=1.11 p=0.304	F(1,21)=0.37 p=0.549
<b>Ant-Post</b> (mm)	3.5 ±1.4	4.7 ±2.2	3.2 ±0.9	4.2 ±2.1	F(1,21)=12.4 5 p=0.002	F(1,21)=1.99 p=0.173	F(1,21)=0.06 p=0.808
<b>Speed</b> (mm/s)	8.3 ±2.5	8.8 ±2.4	8.8 ±2.5	8.9 ±3.3	F(1,21)=0.69 p=0.416	F(1,21)=1.11 p=0.304	F(1,21)=0.37 p=0.549
<b>Speed variability</b> (mm <sup>2</sup> /s <sup>2</sup> )	38.6 ±34.4	40.8 ±22.3	39.5 ±24.5	47.0 ±42.6	F(1,21)=0.94 p=0.343	F(1,21)=0.60 p=0.449	F(1,21)=0.32 p=0.581
<b>Romberg index</b>	2.2 ±0.8	2.0 ±1.1	1.9 ±0.6	2.0 ±0.7	F(1,21)=0.01 p=0.921	F(1,21)=0.84 p=0.370	F(1,21)=0.78 p=0.386
<b>Length /Area ratio</b> (mm <sup>-1</sup> )	2.2 ±0.7	1.5 ±1.0	2.6 ±0.8	1.8 ±1.2	F(1,21)=24.93 p<0.001	F(1,21)=6.0 p=0.023	F(1,21)=0.08 p=0.775

Values are mean ± SD. Ant-Post, standard deviation in antero-posterior plane of CoP displacement length; Romberg index is the ratio between measured surface with eyes closed and eyes opened.

**Table 2.** Sleep recordings, sleep quality, sleepiness and symptoms at sea level and at altitude, following zolpidem or placebo administration.

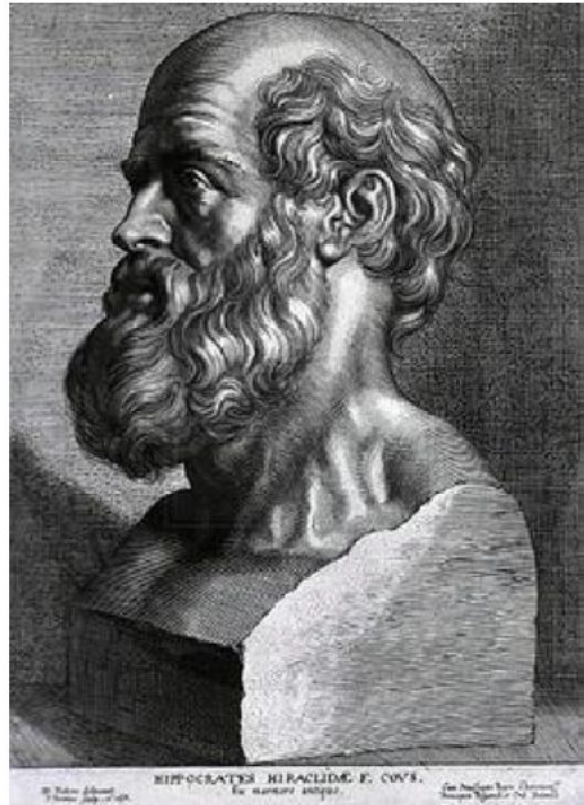
	Sea level Placebo	Sea level Zolpidem	Altitude Placebo	Altitude Zolpidem	Main treatment effect	Main altitude effect	Interaction altitude x treatment
<b>AHI</b> (events/h)	5.6 ±3.9	8.3 ±6.5	27.0 ±33.0	22.6 ±31.0	F(1,21)=0.06 p=0.805	F(1,21)=8.98 p=0.007	F(1,21)=1.20 p=0.285
<b>ODI</b> (events/h)	2.8 ±3.8	4.6 ±5.8	50.4 ±46.9	28.9 ±16.7	F(1,18)=4.94 p=0.039	F(1,18)=30.66 p<0.001	F(1,18)=7.81 p=0.012
<b>Mean SpO<sub>2</sub></b> (%)	94.4 ±1.7	90.8 ±16.9	77.4 ±3.7	77.7 ±4.1	F(1,18)=0.69 p=0.42	F(1,18)=370.93 p<0.001	F(1,18)=0.39 p=0.54
<b>Min. SpO<sub>2</sub></b> (%)	92.8 ±4.0	87.7 ±16.7	70.1 ±5.5	71.0 ±6.8	F(1,18)=0.22 p=0.64	F(1,18)=250.36 p<0.01	F(1,18)=1.93 p=0.18
<b>Sleep quality</b>	2.0 ±0.8	2.8 ±0.4	1.8 ±0.8	2.3 ±0.8	F(1,21)=15.59 p<0.001	F(1,21)=7.55 p=0.012	F(1,21)=0.90 p=0.355
<b>Sleep latency</b>	2.6 ±1.1	1.5 ±0.6	2.7 ±1.2	1.9 ±0.8	F(1,20)=23.16 p<0.001	F(1,20)=0.86 p=0.365	F(1,20)=0.78 p=0.389
<b>Karolinska scale</b>	4.4 ±1.5	5.5 ±1.8	4.5 ±1.7	5.2 ±1.7	F(1,20)=6.90 p=0.016	F(1,20)=0.03 p=0.872	F(1,20)=0.96 p=0.339
<b>Lake Louise Score</b>	1.0 ±1.0	3.2 ±2.8	3.7 ±2.2	4.6 ±2.6	F(1,21)=22.2 p<0.001	F(1,21)=21.83 p<0.001	F(1,21)=0.68 p=0.418
<b>Dizziness</b>	0.0 ±0.2	0.6 ±0.7	0.3 ±0.6	0.5 ±0.8	F(1,21)=11.34 p=0.003	F(1,21)=0.13 p=0.724	F(1,21)=4.04 p=0.057
<b>Ataxia</b>	0.0 ±0.2	0.5 ±0.7	0.4 ±0.6	0.8 ±0.7	F(1,21)=10.66 p=0.004	F(1,21)=6.43 p=0.019	F(1,21)=0.21 p=0.648
<b>Functional estimation</b>	0.2 ±0.4	1.0 ±0.8	0.9 ±0.4	1.5 ±0.7	F(1,21)=22.2 p<0.001	F(1,21)=21.83 p<0.001	F(1,21)=0.68 p=0.418

Values are mean ± SD. AHI, apnea-hypopnea index; ODI, oxygen desaturation index; Mean SpO<sub>2</sub>, mean arterial oxygen saturation; Min SpO<sub>2</sub>, minimum arterial oxygen saturation; Dizziness, ataxia and functional evaluation are clinical assessment of the Lake Louise Score.

**Table S1.** Prefrontal cortex oxygenation measured by near infrared spectroscopy during the cognitive tasks at rest and during exercise, at sea level and at altitude, following zolpidem or placebo administration.

	Sea level Placebo	Sea level Zolpidem	Altitude Placebo	Altitude Zolpidem	Main treatment effect	Main altitude effect	Interaction altitude x treatment
<b>Simon cognitive test at rest</b>							
<b>[HbO<sub>2</sub>]</b> ( $\mu$ M.cm)	0.60 $\pm$ 1.02	0.74 $\pm$ 1.01	1.07 $\pm$ 1.39	1.15 $\pm$ 1.45	F(1,21)=0.15 p=0.70	F(1,21)=5.28 p=0.032	F(1,21)=0.00 p=0.93
<b>[HHb]</b> ( $\mu$ M.cm)	-0.31 $\pm$ 0.33	-0.42 $\pm$ 0.43	-0.08 $\pm$ 0.60	-0.19 $\pm$ 0.46	F(1,21)=0.72 p=0.40	F(1,21)=5.11 p=0.034	F(1,21)=0.00 p=0.99
<b>[Hb<sub>Tot</sub>]</b> ( $\mu$ M.cm)	0.28 $\pm$ 1.03	0.31 $\pm$ 1.19	0.98 $\pm$ 1.72	0.96 $\pm$ 2.04	F(1,21)=0.00 p=0.99	F(1,21)=7.89 p=0.010	F(1,21)=0.01 p=0.94
<b>Simon cognitive test during exercise</b>							
<b>[HbO<sub>2</sub>]</b> ( $\mu$ M.cm)	4.01 $\pm$ 2.54	3.75 $\pm$ 2.78	3.03 $\pm$ 1.95	2.69 $\pm$ 2.02	F(1,21)=0.59 p=0.45	F(1,21)=8.45 p=0.008	F(1,21)=0.02 p=0.89
<b>[HHb]</b> ( $\mu$ M.cm)	0.18 $\pm$ 0.46	0.23 $\pm$ 0.45	0.46 $\pm$ 0.94	0.35 $\pm$ 1.14	F(1,21)=0.07 p=0.79	F(1,21)=1.35 p=0.26	F(1,21)=0.45 p=0.45
<b>[Hb<sub>Tot</sub>]</b> ( $\mu$ M.cm)	4.19 $\pm$ 2.73	3.98 $\pm$ 3.05	3.50 $\pm$ 2.50	3.04 $\pm$ 2.83	F(1,21)=0.52 p=0.48	F(1,21)=3.66 p=0.069	F(1,21)=0.11 p=0.74
<b>Duration-production task at rest</b>							
<b>[HbO<sub>2</sub>]</b> ( $\mu$ M.cm)	0.73 $\pm$ 1.34	0.75 $\pm$ 1.34	1.19 $\pm$ 1.51	1.18 $\pm$ 1.24	F(1,21)=0.00 p=0.99	F(1,21)=2.86 p=0.11	F(1,21)=0.97 p=0.97
<b>[HHb]</b> ( $\mu$ M.cm)	-0.37 $\pm$ 0.45	-0.52 $\pm$ 0.49	-0.07 $\pm$ 0.64	-0.21 $\pm$ 0.66	F(1,21)=2.21 p=0.15	F(1,21)=7.68 p=0.011	F(1,21)=0.01 p=0.96
<b>[Hb<sub>Tot</sub>]</b> ( $\mu$ M.cm)	0.36 $\pm$ 1.39	0.23 $\pm$ 1.56	1.11 $\pm$ 1.82	0.97 $\pm$ 1.44	F(1,21)=0.20 p=0.66	F(1,21)=6.62 p=0.018	F(1,21)=0.00 p=0.98
<b>Duration-production task during exercise</b>							
<b>[HbO<sub>2</sub>]</b> ( $\mu$ M.cm)	5.12 $\pm$ 3.02	4.47 $\pm$ 3.21	3.07 $\pm$ 1.87	3.03 $\pm$ 2.18	F(1,21)=0.65 p=0.43	F(1,21)=19.44 p<0.001	F(1,21)=0.70 p=0.41
<b>[HHb]</b> ( $\mu$ M.cm)	0.37 $\pm$ 0.67	0.34 $\pm$ 0.63	0.60 $\pm$ 1.13	0.45 $\pm$ 1.35	F(1,21)=0.39 p=0.54	F(1,21)=0.67 p=0.42	F(1,21)=0.20 p=0.66
<b>[Hb<sub>Tot</sub>]</b> ( $\mu$ M.cm)	5.49 $\pm$ 3.35	4.82 $\pm$ 3.64	3.67 $\pm$ 2.67	3.48 $\pm$ 3.25	F(1,21)=0.68 p=0.42	F(1,21)=9.38 p=0.006	F(1,21)=0.27 p=0.61
<b>Arterial oxygenation and heart rate at rest</b>							
<b>Mean SpO<sub>2</sub></b> (%)	96.2 $\pm$ 1.1	96.6 $\pm$ 1.4	85.3 $\pm$ 2.6	85.7 $\pm$ 2.0	F(1,21)=1.39 p=0.25	F(1,21)=514.2 p<0,001	F(1,21)=0.05 p=0.83
<b>Heart rate</b> (bpm)	68.1 $\pm$ 8.6	74.7 $\pm$ 10.5	78.7 $\pm$ 9.3	84.8 $\pm$ 12.9	F(1,21)=36.85 p<0,001	F(1,21)=39.51 p<0,001	F(1,21)=0.04 p=0,85
<b>Arterial oxygenation and heart rate during exercise</b>							
<b>Mean SpO<sub>2</sub></b> (%)	96.4 $\pm$ 1.1	96.1 $\pm$ 1.2	79.1 $\pm$ 4.5	79.7 $\pm$ 4.1	F(1,21)=0.36 p=0.56	F(1,21)=402.8 p<0,001	F(1,21)=2.84 p=0.11
<b>Heart rate</b> (bpm)	120.1 $\pm$ 14.1	123.1 $\pm$ 17.3	120.2 $\pm$ 14.0	124.6 $\pm$ 18.1	F(1,21)=4.46 p=0,04	F(1,21)=0.18 p=0.67	F(1,21)=0.31 p=0.59
Values are mean $\pm$ SD. HbO <sub>2</sub> , oxyhaemoglobin; HHb, deoxyhaemoglobin; HbTot, total haemoglobin.							

## SERMENT D'HIPPOCRATE



*En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,*

*Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.*

*Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.*

*Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

*Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.*

*Je garderai le respect absolu de la vie humaine.*

*Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.*

*Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

*Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.*

*Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.*