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寒花开已尽，菊蕊独盈枝。唐. 杜甫 《云安九日》

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CASA 2021 President Report

年终总结

黄建宏，MD

转眼之间，一年就过去。首先，感谢各位会员在过去一年里，给美国华人麻醉医学会（CASA）的支持和帮助，没有大家的支持，我们可能一事无成。虽然我们取得了不小的成绩，但还需要大家继续群策群力，才能把工作做得更好，把 CASA 继续推向新的高度。

请允许我向大家汇报在过去的一年里取得的成果。我们把今年的工作目标定为“推动麻醉教育，促进患者安全”。今年我们完成了许多麻醉教育工作。

CASA 积极组织和参与国际和国内麻醉学教育活动

1）CASA 与新青年麻醉论坛联合举办了产科麻醉急症处理系列公开课讲座

这是一个非常优秀的系列课。是新青年麻醉论坛最受欢迎的公开课之一。CASA 讲师们认真备课，演讲生动，内容非常接地气。每次讲课都吸引了 5-25 万听众。

姚尚龙：中国产科麻醉挑战和对策
黄建宏：产科麻醉应急手册应用
李师阳：植入胎盘麻醉管理
左明章：产科困难气道
徐铭军：羊水栓塞，过敏反应
黄佳鹏：孕产妇心跳骤停
陶为科：孕产妇大出血
李金蕾：局麻药中毒
李韵平：硬膜外的问题和对策
曹锡清：产科全麻，即刻剖宫产
王景平：如何开展模拟演练
郑勤田：胎盘早剥，脐带脱落，宫缩乏力，子宫内翻
彭勇刚：ECMO 在产科麻醉急症的应用
张砥：孕产妇危象：甲状腺危象，高血压危象，酮症酸中毒
胡灵群：主动脉狭窄分娩管理

2）麻醉无界国际热点云端研讨会

CASA 与恒瑞医药合作举办多场麻醉热点云端研讨会。恒瑞&CASA——携手基层 一起强大，是江苏恒瑞医药股份有限公司携手美国华人麻醉医学会（CASA）共同举办的基层讲学活动。在疫情影响下，充分利用多媒体平台，借助网络的力量，加强国内麻醉医师与 CASA 专家的交流，助力中国麻醉基层医生业务技能的提升。

今年总共开展 147 场交流，覆盖了 300 余家医院，参与人数达 5000 人。因为 CASA 讲师们直接与基层医院医生面对面交流，讲师们认真解答他们的问题，广大基层医院医生反应此活动非常接地气，能够实际解决许多临床问题，帮助提高他们的知识和技能。

3）中国医师协会麻醉学医师分会 2021 年年会

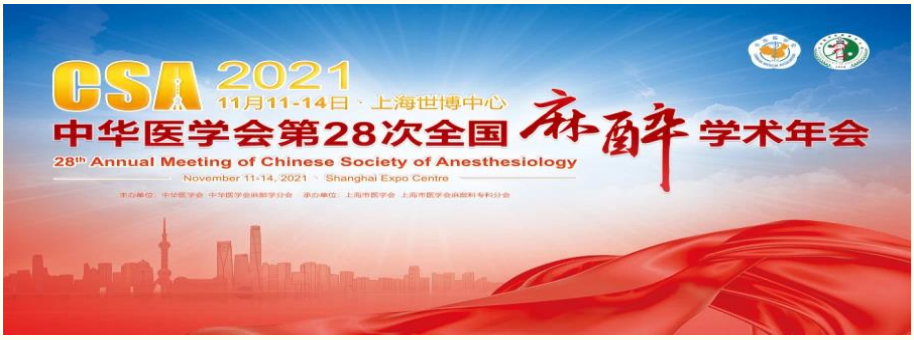
CASA 是中美麻醉界交流合作的平台。受中国医师协会麻醉学医师分会（CAA） 和中华医学会麻醉学分会（CSA）的邀请，我们组织代表团参加了今年的 CAA 与 CSA 的年会。

CAA 年会为 CASA 设置了“心脏麻醉管理”为主题的专门板块。 由于疫情影响，CASA 分会场采用线上录制直播的形式与国内同行进行了交流。 围绕心血管麻醉管理的热门话题展开讨论。 参与会议的六位专家和演讲题目分别为：弗罗里达大学医学院的彭勇刚教授 《围术期房颤和心电装置管理困惑和挑战》，美国路易维尔大学的黄佳鹏教授 《围术期心脏超声在非心脏手术应用最新解读》，美国西弗吉尼亚大学的汪红教授《冠脉支架病人的围术期管理》，美国加州慈善总医院的唐越教授 《右心衰竭的诊断和处理》，宾州州立大学的刘恒意教授 《微创及无创心排出量测定技术之进展》，美国华盛顿大学医学中心的宋萍萍教授《心脏瓣膜病变的麻醉管理》。在三个半小时时间，各位专家围绕上述主题， 给予了认真的演讲，分享了当前心脏麻醉管理最前沿的知识、理念和技术。线上线下听众积极参与，反应热烈。

4）中华医学会麻醉学分会（CSA）2021 年会

因为疫情所致，CSA 会议主要采用线上讲课和线上讨论的形式。CASA 讲师团成员认真准备，提前录制讲课视频，年会上播放，并参加了线上讨论。参加会议的 CASA 成员及他们的题目：

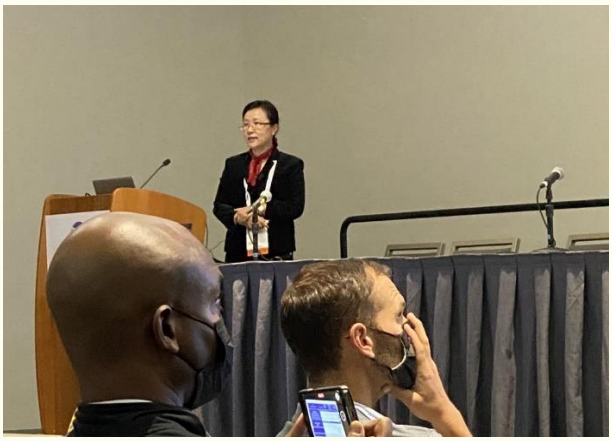
李金蕾：全方位围术期疼痛管理：acute and transitional pain service
麻浩波：如何利用医学大数据做研究
黄建宏：麻醉与肿瘤治疗
张晓燕：当前麻醉质量监测与质量提升的关系
曹锡清：恶性高热和热休克有关系吗?



5）美国麻醉医生 2021 年会

CASA 不仅在国际交流上取得丰硕成果，也在美国的麻醉教育贡献了很多。他们的成果也是有目共睹的。CASA 成员们也参加在美国 San Diego 举行的美国麻醉医生年会。大家都很高兴能参加疫情后首次 ASA 现场年会。值得提出的是，几位成员都是 ASA 年会的讲者和主持人：

李金蕾：Moderator and lead speaker,
题目: Nerve blocks in total hip arthroplasty: are they necessary



宋萍萍，彭勇刚:Moderator/Speaker
Arrest? Open the Chest! Protocol for Resuscitation of Patients Who arrest after cardiac surgery

王謐：Workshop Instructor
题目：Invasive airway hands on simulation workshop

李锋华：PBLD Moderator
Anesthesia care of geriatric patient for right hip hemiarthroplasty

这些学术活动的内容非常有吸引力，会场上坐无虚席，内容丰富精彩。坚信以后 ASA 年会上会有更多的 CASA 成员的讲座。

CASA 一直和 ASA 一致，鼓励会员积极参与医院和各级协会的领导工作。许多 CASA 会员都是 ASA 的 Delegates 或者是 Committee members。他们积极参与领导和政策的决定和实施。年会期间 CASA 成员也参加 ASA Leadership and Committee Meetings， 参与 ASA 政策的制定。

曹锡清医生参加了 ASA Reference committee scientific affair 听证会，参与发言及修订了 ASA 年会草案。参加 ASA house of delegate’s 现场会议。

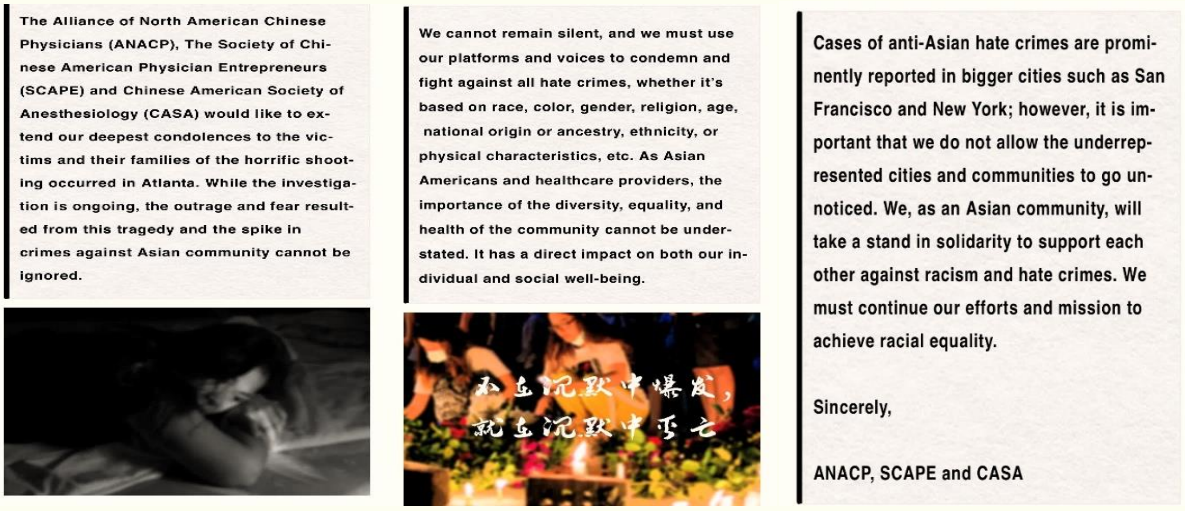
坚信以后会有更多的 CASA 成员成为全国，州，当地的麻醉或医学协会的领导。

CASA 积极参与和组织“制止仇恨亚裔的犯罪”活动

然而从 COVID-19 爆发以来，针对亚裔美国人的袭击和仇恨犯罪上升了 150％以上，在全国范围内达到了 3000 宗。3 月 16 日，美国佐治亚州亚特兰大市发生枪击案，事件造成 8 人死亡，其中 6 名是亚裔女性。反亚裔的仇恨犯罪和暴力行为的激增是由于公开的偏激言论、种族主义、仇外心理和历史悠久的无知所致。

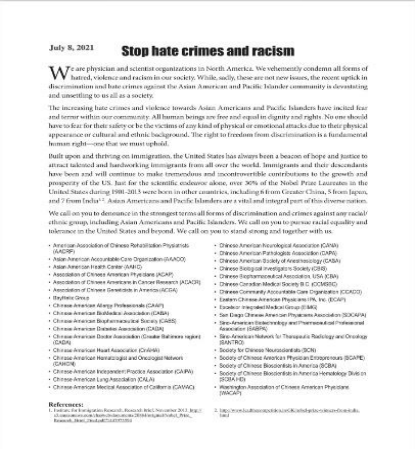
为了保护亚裔美国人的生命和权利，我们不能对任何仇恨和暴力保持沉默。我们必须团结起来，站出来表达我们的诉求。作为亚裔医学专业协会之一，我们将团结一致打击种族主义和仇恨犯罪，追求种族平等。

3/22/2021, 美国华人麻醉医学会（CASA）联合北美华医联盟（ANACP），美国华人执业医师协会（SCAPE）在第一时间里发布了联合声明。呼吁社会：作为一个亚裔社区，我们将团结并相互支持，反对种族主义和仇恨犯罪。我们必须继续我们的努力和使命，以实现种族平等。



为了进一步扩大影响，CASA 积极加入由美国华人血液和肿瘤专家协会发起的让更多科技界的的同仁们也加入的“制止仇恨亚裔的犯罪”的活动。二十多个亚裔医学组织参加，

把制止仇恨亚裔的声明发表到著名的《Science 》和《Nature》的杂志。让更多科学界和医学界的同仁们能和我们一起参加“制止仇恨亚裔的犯罪”的活动。让不同种族、肤色、性别、宗教、年龄、国籍或血统的科学家和医务人员都使用自己的平台和声音谴责和打击所有仇恨犯罪。


July 8, 2021

Stop hate crimes and racism

We are physician and scientist organizations in North America. We vehemently condemn all forms of hatred, violence and racism in our society. While, sadly, these are not new issues, the recent uptick in discrimination and hate crimes against the Asian American and Pacific Islander community is devastating and unsettling to us all as a society.

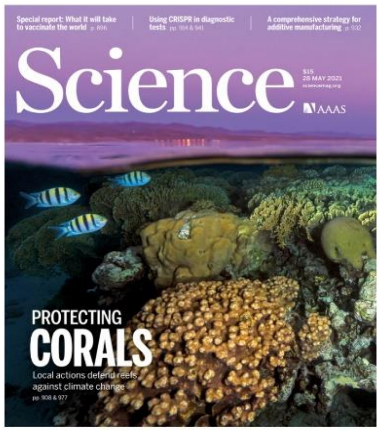
The increasing hate crimes and violence towards Asian Americans and Pacific Islanders have incited fear and former within our community. All human beings are free and equal in dignity and rights. No one should have to fear for their safety or be the victims of any kind of physical or emotional attacks due to their physical appearance or cultural and ethnic background. The right to freedom from discrimination is a fundamental human right—one that we must uphold.

Built upon and thriving on immigration, the United States has always been a beacon of hope and justice to attract talented and hardworking immigrants from all over the world. Immigrants and their descendants have been and will continue to make tremendous and incontrovertible contributions to the growth and prosperity of the US. Just for the scientific endeavor alone, over 36% of the Nobel Prize Laureates in the United States during 1901-2015 were born in other countries, including 6 from Greater China, 5 from Japan, and 7 from India[1]. Asian Americans and Pacific Islanders are a vital and integral part of this diverse nation.

We call on you to denounce in the strongest terms all forms of discrimination and crimes against any racial/ethnic group, including Asian Americans and Pacific Islanders. We call on you to pursue racial equality and tolerance in the United States and beyond. We call on you to stand strong and together with us.

- American Association of Chinese Rehabilitation Physicians (AACRP)
- Asian American Accountable Care Organization (AAACO)
- Asian American Health Center (AAHC)
- Association of Chinese American Physicians (ACAP)
- Association of Chinese Americans in Cancer Research (ACACR)
- Association of Chinese Geneticists in America (ACGA)
- Rhythmi Group
- Chinese American Allergy Professionals (CAAP)
- Chinese American Audiologist Association (CAAA)
- Chinese American Biopharmaceutical Society (CABS)
- Chinese American Diabetes Association (CADA)
- Chinese American Doctor Association (Greater Baltimore region) (CADA)
- Chinese American Heart Association (CAHA)
- Chinese American Hematologist and Oncologist Network (CAHON)
- Chinese American Independent Practice Association (CAIPA)
- Chinese American Lung Association (CALA)
- Chinese American Medical Association of California (CAMAC)
- Chinese American Neurological Association (CANA)
- Chinese American Pathologists Association (CAPA)
- Chinese American Society of Anesthesiology (CASA)
- Chinese Biological Investigators Society (CBIS)
- Chinese Biopharmaceutical Association, USA (CBA)
- Chinese Canadian Medical Society in D.C. (CCMSDC)
- Chinese Community Accountable Care Organization (CCACO)
- Eastern Chinese American Physicians PA, Inc. (ECAP)
- Excelsior Integrated Medical Group (EIMG)
- San Diego Chinese American Physicians Association (SDCAPA)
- Sino-American Biotechnology and Pharmaceutical Professional Association (SABPA)
- Sino-American Network for Therapeutic Radiology and Oncology (SANTRO)
- Society for Chinese Neuroscientists (SCN)
- Society of Chinese American Physician Entrepreneurs (SCAPE)
- Society of Chinese Bioscientists in America (SCBA)
- Society of Chinese Bioscientists in America-Hematology Stem in (SCBA-HS)
- Washington Association of Chinese American Physicians (WACAP)

References:



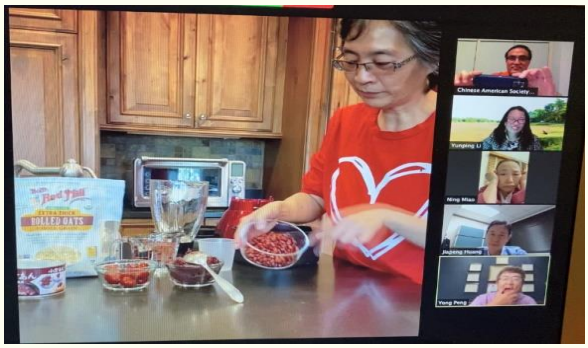
CASA 关注会员 Wellness，积极组织促进会员交流沟通活动

疫情发生后，大家面对面交流的机会越来越少。许多活动都从线下转到线上。疫情限制了我们的交往，但是没有阻挡我们之间的交流。CASA 也充分利用 ZOOM 平台积极组织多场线上会员交流活动。

1）2021 CASA 线上春节联欢会

CASA 在二月十三日组织了 2021 年线上迎新春活动！虽说是线上，大家相互认识，相互交流，相互问候和祝 福。ASA President-Dr. Philip，中华医学会麻醉学分会主席-黄宇光教授和中国医师协会麻醉学医师分会执行主席-于布为教授分别在各自的视频里祝所有美国华人麻醉医生们新年快乐，阖家欢乐。

参加活动者包括在美国行医几十年的华人老麻醉医生，中生代的麻醉中坚力量和尚未毕业的住院医生、fellow 等新一代年轻的麻醉医生—他们是美国华人麻醉界的的新鲜血液和我们未来的希望！晚会内容包括音乐，舞蹈，书画，美食，摄影等。预计两小时的迎新活动延至四小时才完美落幕。



2）CASA 聊聊麻醉：困惑和策略

我们 CASA 许多麻醉医生大都行医超过 20 年，并且 2/3 的医生年龄也超过 50 岁。许多人正在考虑走入人生的下一个阶段。他们也积累了不少宝贵的经验。为了不让这些经验和知识流失，让他们把这些经验分享给大家，CASA 决定开创周末线上交流活动：聊聊麻醉：困惑和策略。在轻松愉快的氛围下大家讨论交流一些临床常见病症，互相学习各自的处理和治疗心得。

第一期由前会长刘恒意教授主持，题目是术中呃逆。大家讨论了术中呃逆原因及其治疗办法。这些知识和经验在我们传统麻醉教科书里都找不到的。可以说是 CASA 成员总结出来的独特经验。

第二期由 CASA 副会长张晓燕主持，题目是麻醉医生如何减缓下来。我们 CASA 成员中许多人正在考虑如何走入人生的下一个阶段：即分阶段逐渐减缓工作步伐或考虑退休。大家积极讨论如何从心理或生理上顺利、平稳地过渡这一时期。有许多非常宝贵的经验对许多人都是可以选择和应用的。尤其是工作减缓对自己的身心健康的影响极大。是一个非常有针对性和实用性的题目。

第三期由 CASA 前会长汪红和 ICAA 的孟令忠教授共同主持，题目是术中低血压。这是一直以来困惑大家的问题。我们还邀请了 ICAA 的左志义教授参加了讨论。这也是自疫情以来，CASA 和 ICAA 会员首次一起互动交流的活动。大家热烈讨论了术中低血压的定义，左志义教授说这个困惑在 20 多年前他做住院医生时就在争论，现在还在争论。孟令忠教授最近发表文章提出应该叫 Concerning 低血压， 而不是简单给个数字。彭勇刚教授讲解低血压对心肌的影响，黄佳鹏教授介绍了 HPI（Hypotension Prediction Index）麻醉的研究

和将来的应用，李成付教授介绍他在 Washington University 做近 10 年骨科麻醉主任的临床经验。仲巍教授讲解低血压对儿科麻醉的影响。

大家也分享如何与外科医生沟通的技巧，如何让外科医生满意， 也还能保护患者安全。正如高卫东教授和苗宁主编指出：沟通是消除麻醉医生和外科医生术中低血压要求误解的关键措施。大家热烈提问题和分享讨论自己的病例。有许多中国国内的专家也参加了活动。这个活动充分体现了华人麻醉医生的凝聚力。

孟令忠和左志义教授指出 CASA 和 ICAA 一起合作交流的重要性， 希望将来能举办更多的一起合作交流的活动。

3）CASA ASA 聚会

托新冠疫苗的福，CASA 2021 线下聚会能够顺利进行。ASA 举行了自新冠流行以来首次线下会议，参会的 CASA 会员大多数完成了新冠疫苗接种，并且都接种了第三针加强针。这次 CASA 聚会人数少了一些，但是参加人的热情也不亚于以前的盛会。大家一起畅聊了自己如何抗病毒，解救患者，调整自身，适应新环境。许多在加州工作的会员不辞劳苦，驰车赶来参加聚会。新老朋友一起欢聚，回忆过去，互相交流下一步的工作和生活的计划。这次聚会是由 CASA 副会长张晓燕精心组织和计划的。参会人员是从美国各地到 San Diego 参加美国 ASA 年会的会员们。



今年 ASA 年会增加一项 Presidential Reception 活动，许多参会的 CASA 会员都参加了此次活动，大家都给予很高的评价，非常 Fun, 表示下次还要参加。

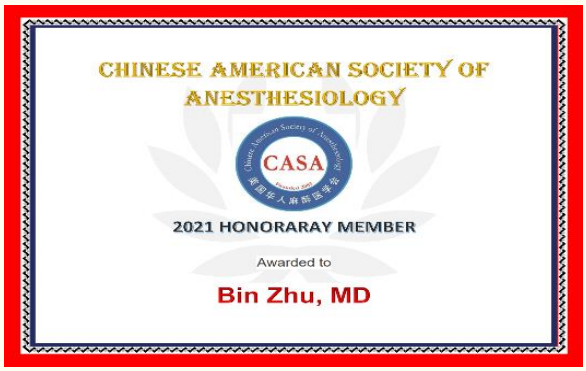
4) CASA Bulletin of Anesthesiology 最佳作者评选：

今年 CASA 首次创立了 CASA Bulletin of Anesthesiology 最佳作者奖。多年来在各位编辑的共同努力下，杂志内容越来越丰富，成为中美麻醉学术交流的平台。也为会员们提供了一个平台总结自己的经验，与分员们一起分享和讨论各种病例。创立最佳作者奖可以进一步鼓励大家踊跃投稿，把杂志推向更高层次。

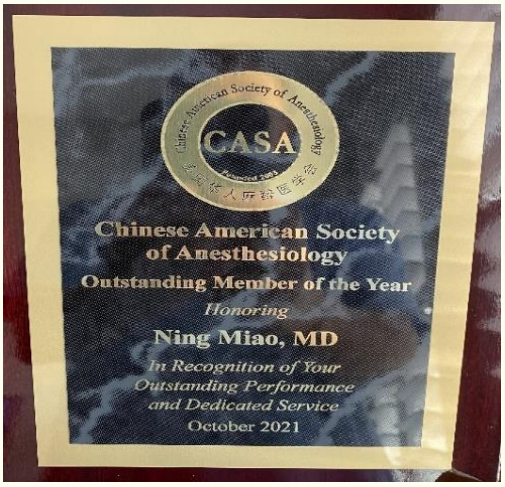
CASA 2021 年度获奖名单：

Honorary Member:

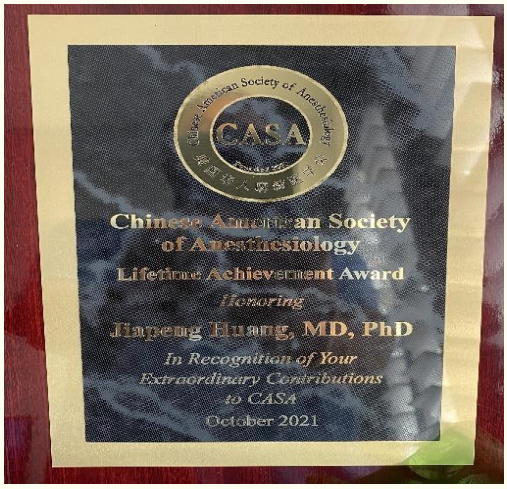
张惠：空军军医大学第三医院麻醉科　　朱斌：上海嘉会国际医院麻醉科



Outstanding Member of the Year
苗宁：Ning Miao, MD
CASA Bulletin Editorial Board



Lifetime Achievement Award:
黄佳鹏：Jiapeng Huang, MD, PhD



Presidential Resident Awards:
First place: 丁敏哲 Andrewston Ting,DO

Second Place: 蒋天宇 Tianyu Jiang,DO

Presidential CASA Bulletin of Anesthesiology Best Author Awards:

第一名：Lin Tang
第二名：Jonathan Chen, Weidong Gao, Jiahao Zhang, 任宪凤

在过去的一年里，我们取得了许多优秀的成绩，但是还有许多任务需要完成。十分感谢各位的无私奉献和帮助。希望大家能够一如既往，支持曹锡清领导 CASA 下一年的工作，把 CASA 推向更高的层面。

主编之言

急、慢性疼痛和镇痛治疗

苗宁, MD

疼痛是由组织损伤导致的不愉快的感觉和情绪反映。疼痛可分为急性疼痛和慢性疼痛。急性疼痛为近期突然发生且持续时间较短的疼痛，常为许多疾病的症状， 与手术、创伤、组织损伤或某些疾病状态有关；慢性疼痛持续反复时间长，往往持续三个月以上且难以缓解。长期的不可治愈的慢性病所致的持续性疼痛会引起一系列病理生理变化，影响患者的情绪，引起或加重精神紧张，抑郁、焦虑。

目前的共识将疼痛的机理分为：1.伤害性，2.外周神经性，3. 中枢性疼痛。伤害性疼痛与外周神经对炎症、机械或缺血性刺激的反应有关；外周神经性疼痛是由周围神经系统的原发病变或功能障碍引发；而中枢性疼痛是由中枢神经系统 (CNS) 的原发病变或功能障碍引发的疼痛。

镇痛治疗减轻病患的生理和心理疼痛不可或缺又十分棘手，许多急慢性疼痛患者的镇痛治疗还差强人意。现多用多模式镇痛方法控制疼痛。联合应用不同镇痛技术或作用机制不同的镇痛药，作用于疼痛传导通路的不同靶点，发挥镇痛的相加或协同作用，可使每种药物的剂量减少，副作用减轻。1.镇痛药物治疗如阿片类药物，局部麻醉剂，解热镇痛药，抗忧郁药以及医用大麻等；2.物理治疗：冷疗，热疗，瑜伽，激光，按摩，透入疗法，脉冲电磁疗法和冲击波治疗；3.心理疗法：暗示， 分心疗法，认知行为疗法，支持心理疗法，催眠疗法等；4.针灸也可一定程度控制急慢性疼痛；5.微创手术治疗如射频神经调节，低温等离子椎间盘消融，椎间孔镜技术，脊髓刺激术和神经阻滞联合消炎镇痛液注射均可减少慢性疼痛或改善生活质量。

在现代医学高度发展的今天，临床麻醉医生恰当的镇痛治疗以有效减轻或消除患者围术期的急性不良感受，是我们作为麻醉医生的共识；而麻醉疼痛科医生的主要职责偏重于使用多重理论、方法和不断发展的科学技术缓解或消除病患的慢性疼痛，改善病患的生理和心理负荷，增强生活品质，更是我们今后不断探索和实践的重中之重。

本期专题

COVID-19 Pain

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Introduction

After initial reports of COVID-19 in late 2019, the virus has since spread rapidly across the U.S. and the globe. In March 2020, COVID-19 was officially declared a pandemic by the World Health Organization, and since then, 258 million individuals worldwide have been infected by the virus and 5.17 million people have died. In the U.S., more than 47 million people have been infected and more than 760 thousand people have died.[1] Although COVID-19 mainly affects the respiratory system and can lead to multi-organ damage in the body, little is known about its impacts on pain. Pain is an unpleasant sensory and emotional experience potentially related to tissue damage. Clinical manifestations of COVID-19 pain vary from headache, abdominal pain, arthralgia, to myalgia. Myalgia, or muscle pain, is one of the most frequent symptoms among COVID-19 patients, while neuropathic pain is rarely reported by COVID-19 patients.[2]

Incidence

COVID-19 can affect nearly every organ system, causing cardiovascular, gastrointestinal, musculoskeletal, respiratory, and neurologic symptoms. It can affect the nervous system (headache, neuropathic pain), digestive system (abdominal pain, visceral pain), musculoskeletal system (myalgia/arthralgia) and cardiovascular system (chest pain). Clinical manifestations of COVID-19 pain have been reported to vary from headache, abdominal pain, arthralgia, myalgia, bone pain and or neuropathic pain. Muscle pain or myalgia is one of the most frequent symptoms among COVID-19 patients. The incidence rates of COVID-19 pain vary from 1.7–33.9% for headache, 0.7–47.1% for sore throat, 1.5–61.0% for myalgia/arthralgia, 1.6–17.7% for chest pain, and 1.9–14.5% for abdominal pain, etc.[3]

Patients with COVID-19 exhibit various symptoms, such as fever, cough, dyspnea, muscle pain, headache, sore throat, chest pain, and abdominal pain at 2–14 days.[4] Huang et al reported on the presence of clinical symptoms at the onset of illness in patients with COVID-19, in which fever was the most common symptom (98%), followed by cough (76%), dyspnea (55%), muscle pain or fatigue (44%), sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3%).[5] Guan et al found that the common pain symptoms include myalgia or arthralgia (14.9%), sore throat (13.9%), and headache (13.6%).[6] Beside respiratory symptoms, pain symptoms such as headache, sore throat, myalgia/arthralgia, chest pain, and abdominal pain are also common in patients with COVID-19.

Mechanism

SARS-CoV-2 is an RNA virus with a viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor on human cells Fig. 1.[7] There is high expression of the ACE2 receptor in lung epithelial cells as well as in the heart, kidney, pancreas,

spleen, gastrointestinal system, bladder, cornea, and blood vessels.[8, 9] The ACE2 receptor is also found in the central and peripheral nervous systems and in skeletal muscle.[10],[11] Viral replication within human host cells is followed by viral release through cell destruction. In addition, SARS-CoV-2 activates an inflammatory response (both innate and adaptive immune responses) which can result in a cytokine storm and ultimately multi-organ injury.[8, 9]

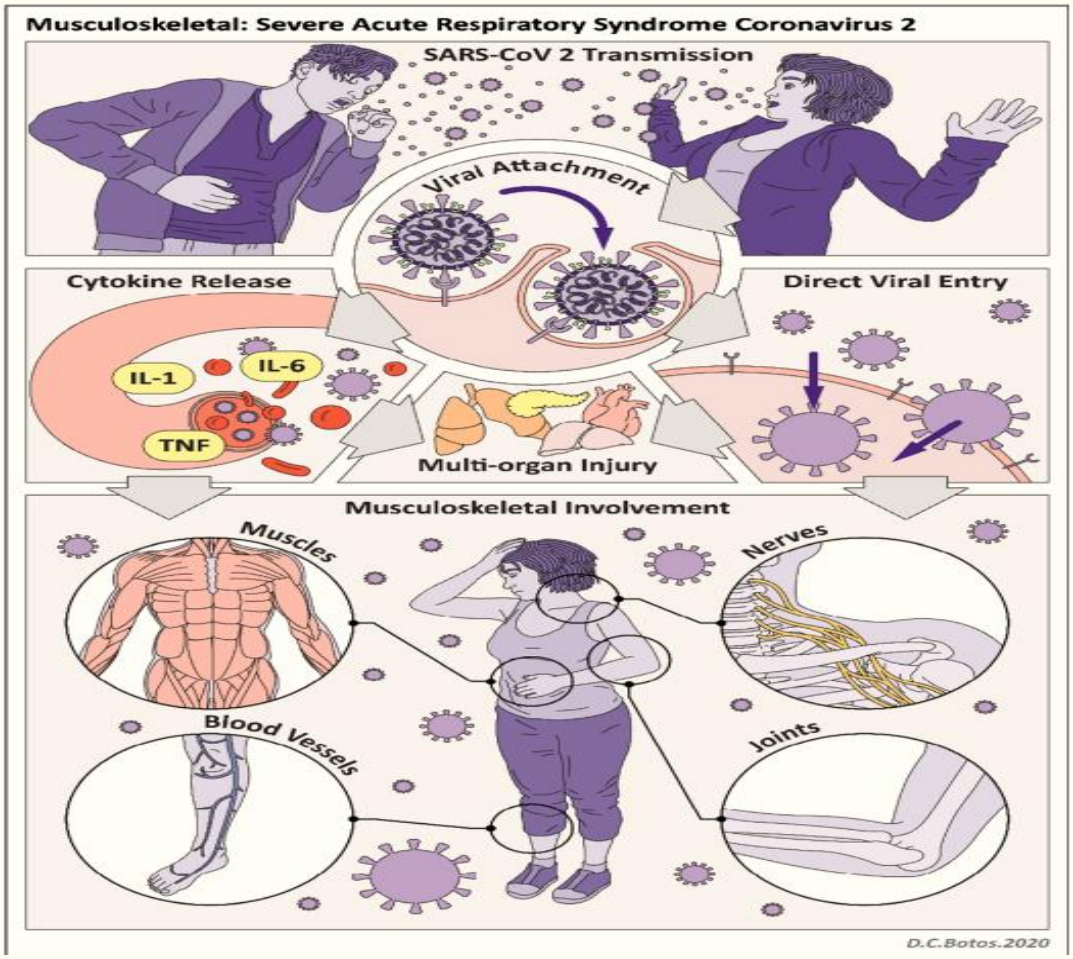

Fig. 1 Multi-organ injury and musculoskeletal involvement in COVID-19 [7]

The SARS-CoV-2 virus not only invades the respiratory system and causes fever, cough, sore throat, and other pneumonia associated symptoms, but also infects other systems in humans and results in corresponding symptoms, including the nervous system (headache, dizziness, and confusion), digestive system (diarrhea, abdominal pain, and loss of appetite), and cardiovascular system (chest pain, and cardiac injury).[5, 12]

Imaging

There have been emerging reports; however, of an array of neuromuscular and rheumatologic complications related to COVID-19 infection and disease course including myositis, neuropathy, arthropathy, and soft tissue abnormalities. Multimodality supports diagnosis and evaluation of musculoskeletal disorders in COVID-19 patients, Table 1.[7]

Organ system	Imaging modalities	Imaging findings
Muscle	MRI +/− contrast	Muscle edema, necrosis
		Muscle atrophy
	Ultrasound	Diaphragm dysfunction
Nerve	MR neurography	Nerve enlargement, signal hyperintensity, loss of fascicular architecture
		+/− muscle denervation
	High-resolution ultrasound	Nerve enlargement, hypoechogenicity, loss of fascicular architecture
Joints	MRI +/− contrast	Joint effusion with enhancement, +/− erosions
	Ultrasound with Doppler	Synovitis, hyperemia
Soft tissues	MRI, CT, ultrasound	Hematomas, gangrene, "COVID toes," atypical pressure ulcers from prone positioning
Bone	Radiography, CT, MRI	Osteoporosis, osteonecrosis

Table 1. Imaging of musculoskeletal involvement in COVID-19.[7]

Multimodality imaging, including radiography, CT, ultrasound, and MR imaging, can play an important role in the diagnosis and evaluation of COVID-19-related musculoskeletal pathology. Imaging can be utilized for initial diagnosis as well as for follow-up evaluation to assess recovery versus progression of the disease.

Long COVID

The sequelae after recovery from acute COVID-19 have been widely reported [2–12] and have become an increasing concern. Many studies show that a variety of symptoms can be persistent after the acute infection of COVID in many patients who have had COVID-19. This condition is known as Long COVID. The National Institute for Health and Care Excellence (NICE) defines Long COVID as the symptoms that continue or develop after an acute COVID-19 infection and which cannot be explained by an alternative diagnosis. This ongoing symptomatic COVID-19 is from four to 12 weeks post-infection. The Post-Covid-19 Syndrome is beyond 12 weeks post-infection.[13] The National Institutes of Health (NIH) uses the US Centers for Disease Control and Prevention's (CDC) definition of long covid, which describes the condition as sequelae that extends beyond four weeks after the initial infection.[14]

Studies around the world have reported various incidence rates for Long COVID with different follow-up examination times after the acute infection, including 76% of people at 6 months,[15] 32.6% at 60 days,[16] 87% of people at 60 days,[17] and 96% of people at 90 days.[18]

People with Long COVID exhibit involvement and impairment in the structure and function of multiple organs.[19-22] Numerous symptoms of Long COVID have been reported and attributed to various organs, an overview of which can be seen in Fig. 2.[23] Long-term symptoms following COVID-19 have been observed across the spectrum of disease severity.

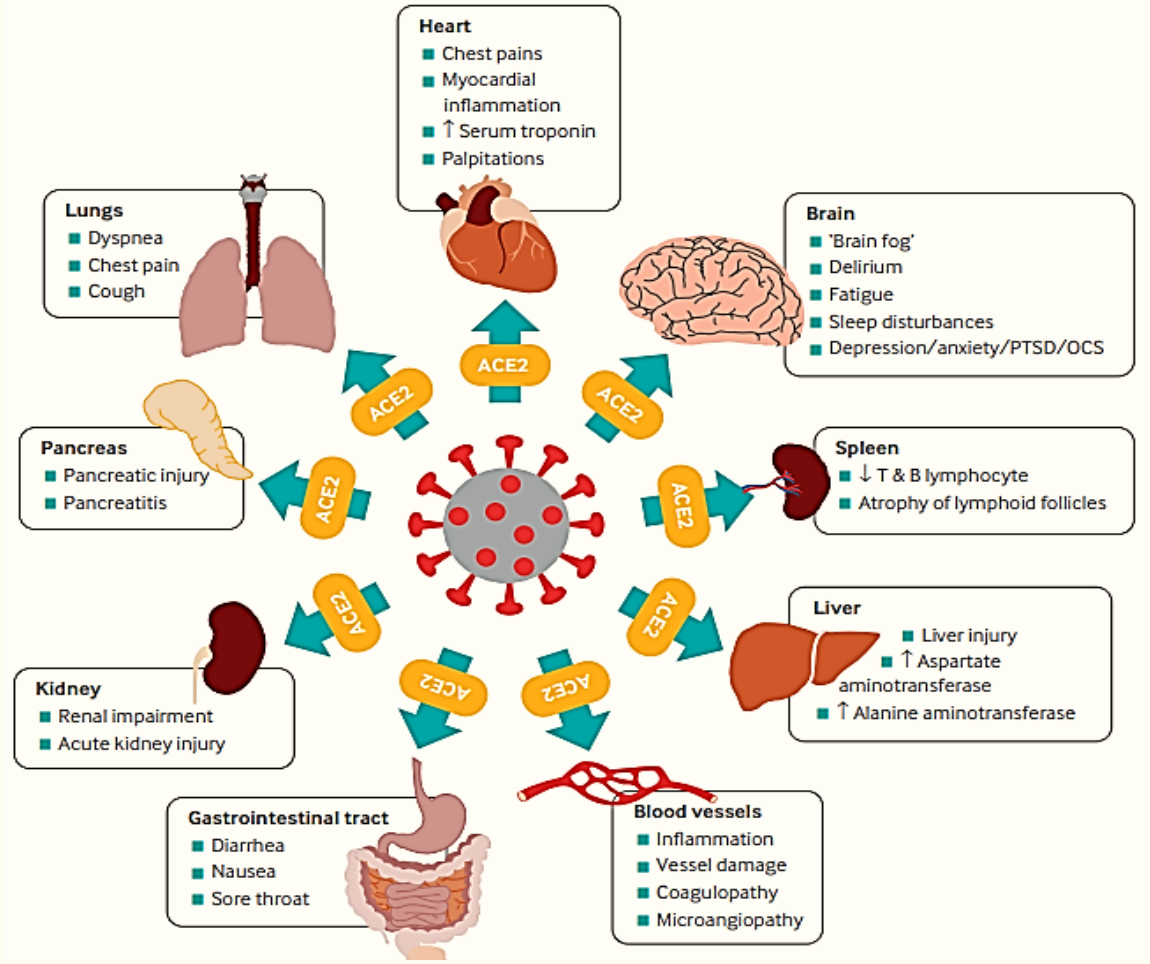

Fig. 2 Multi-organ complications of COVID-19 and long covid. The SARS-CoV-2 virus enters the cells of multiple organs via the ACE2 receptor. Once these cells have been invaded, the virus can cause a multitude of damage ultimately leading to numerous persistent symptoms.[23]

The long-term sequelae of COVID-19 in the central nervous system, Fig 3: (A) The long-term immune response activates glial cells which chronically damage neurons. (B) Hyperinflammatory and hypercoagulable states lead to an increased risk of thrombotic events. (C) Blood-brain barrier damage and dysregulation results in pathological permeability, allowing blood derived substances and leukocytes to infiltrate the brain parenchyma. (D) Chronic inflammation in the brainstem may cause autonomic dysfunction. (E) The effects of long COVID in the brain can lead to cognitive impairment. Also, a range of central, peripheral, and psychological factors may cause chronic fatigue in long COVID. Chronic inflammation in the brain, as well as at the neuromuscular junctions, may result in long term fatigue. In skeletal muscle, sarcolemma damage and fiber atrophy and damage may play a role in fatigue.[23] These mechanisms causing post-COVID cognitive impairment and fatigue could be linked to and possibly cause post-COVID pain problems. Exaggerated levels of systemic inflammation, observed in some patients as a “cytokine storm,” in addition to activation glial cells, poses a substantial risk to the brain and central nerve system, even in peripheral nerve system and musculoskeletal tissues to increase the likelihood of neurological manifestations.[24]

These have led to speculation of potential neurotropism, with both muscle and neural tissue expressing angiotensin-converting enzyme 2 (ACE2) receptor, and COVID-19 virus is also associated with neural injury, including axonopathic polyneuropathy.[25]

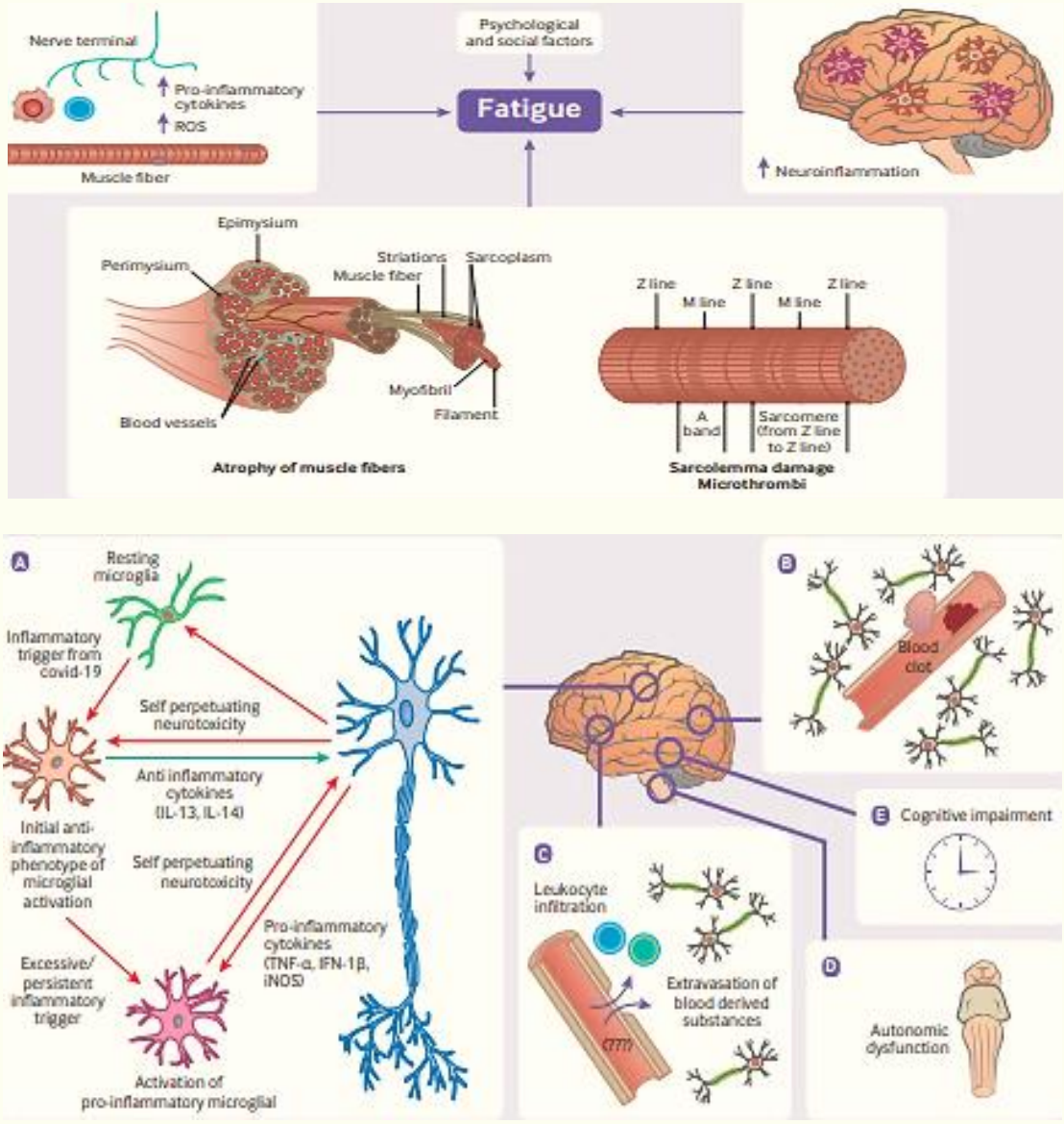

Fig. 3 Long term sequelae of COVID-19 in the central nervous system and possible mechanisms causing Post-COVID-19 fatigue.

Many reports have now emerged on the post-acute infectious consequences of COVID-19, with studies from the United States, Europe and China reporting outcomes for those who have survived an acute COVID-19 infection. The findings from studies reporting outcomes in ongoing symptomatic post COVID-19 and long COVID, and post-COVID-19 syndrome are summarized in Table 2.

Author	# of subjects	Hospitalized or Not	Type of Study	Time to Assessment	Pain Symptoms %
Carfi A, et al, 2020 [26]	143	Hospitalized	Case series	60.3 days after onset	fatigue (53.1%); joint pain (27.3%); chest pain (21.7%)
Dennis A, et al, 2020 [27]	201	Hospitalized: 37; not: 164	Cross sectional (analytic)	140 days after onset	fatigue (98%); muscle ache (87.6%); headache (82.6%); joint pain (78.1%); chest pain (73.6%); sore throat (71.1%)
Tenforde MW, et al, 2020 [28]	274	Non-hospitalized	Cross sectional (survey)	14-21 days after onset	Fatigue (38%); headache (18%); body ache (20%); sore throat (18%); chest pain (20%); abdominal pain (18%)
Cruz RF, et al, 2020 [29]	119	Hospitalized	Cohort Study	4-6 weeks post discharge	Fatigue (67.8%); pain (49.5%)
Valiente-De S, ∈ al, 2020 [30]	82	Non-hospitalized	Observational Study	12 weeks after onset	chest pain (25.9%); headache (9.3%); arthromyalgia (2.8%); anxiety (6.4%)
Sudre CH, et al, 2020 [31]	4182	13.9% required hospital treatment, 86.1% required no hospital treatment	Cohort Study	28 days after onset	fatigue (97.7%); headache (91.2%)
Klein H, et al, 2020 [32]	112	Hospitalized: 6, not: 106	Cross sectional (survey)	6 months after onset	fatigue (20.5%); muscle aches (7.14%); headaches (3.57%)
Eiros R, et al, 2020 [33]	139	Hospitalized: 23, Not: 116	Cross sectional (analytic)	10.4 weeks after onset	No symptoms (34%); fatigue (27%): headache (5%); sore throat (5%); abdominal pain (4%); joint pain (2%); chest pain (19%); pericarditis-like chest pain (13%)
Xiong Q, et al 2020 [34]	538	Hospitalized	Cohort study	97 days post-discharge	General symptoms (49.6%); physical decline/fatigue (28.3%); myalgia (4.5%); arthralgia (7.6%); chest pain (12.3%); throat pain (3.2%); psychosocial symptoms (22.7%); depression (4.3%); anxiety (6.5)
Kamal M, et al, 2020 [35]	287	Hospitalized: 14, Not: 273	Cross sectional (survey)	Unclear	Fatigue (72.8%); anxiety (38%); joint pain (31.4%); continuous headache (28.9%); chest pain (28.9%); depression (28.6%); migraine (2.8%); stroke (2.8%)

Poyraz BC, et al. 2020 [36]	284	Hospitalized: 112, Not: 169	Cross sectional (survey)	50 days following diagnosis	fatigue (40%); muscle aches (22%); headache (17%); light-headedness (7%); numbness and tingling sensations on the skin (6%); chest pain (3%)
Landi F, et al, 2020 [37]	131	Hospitalized	Cohort study	55.8 days after onset	cough (16.7%); fatigue (51.1%); headache (10.6%); joint pain (25.1%); sore throat (6.8%)
Carvalho-Schneider C, et al, 2020 [38]	150	Hospitalized: 53, Not: 97	Cohort study	30 days after onset	chest pain (18%); arthralgia (9.8%)

Table 2**:** Summary of studies that have shown persisting pain symptoms for patients post COVID 19 infection, or during long COVID

A cohort study published in August 2021 investigates 1276 COVID-19 hospital survivors (median age 59 years) at a median follow-up time of 6 months after symptom onset and up to 12 months, advancing our understanding of the nature and extent of long COVID. This study showed matched COVID-19 survivors (compared community-dwelling adults without SARS-CoV-2 infection) at 12 months had more problems with mobility, pain or discomfort, and anxiety or depression, and had more prevalent symptoms than did controls, as almost half of the patients reported having at least one symptom, such as sleep difficulties, palpitations, joint pain, or chest pain, at 12 months.[39] It is noteworthy that pain symptoms were more frequently reported at 12 months than 6 months, as joint pain increased from 12% to 18%, myalgia from 3% to 6%, headaches from 2% to 5%, pain and discomfort from 26% to 42%. The study shows that for many patients, full recovery from COVID-19 will take more than 1 year and raises important issues for health services and research.

Treatment

The treatment needs of COVID-19 survivors are not yet fully understood and appreciated. It is now clear that COVID-19 itself is associated with painful symptoms, including myalgia, arthralgia, abdominal pain, headache, and chest pain. Even those not admitted to critical care environments, may have pain requiring opioids for symptom management.[40] Although the acute challenges of managing COVID-19 have been significant, it may be the long-term effects, including pain, which will have a greater impact on survivors and society. Understanding post-COVID-19 effects and ensuring a strong evidence base for how to manage and treat these patients is vital for healthcare and social care systems and even for policy makers.[25]

Future Study

In order to improve the diagnosis and treatment of COVID-19 pain, prevent it from happening, and improve a patient's quality of life, we must understand more about the mechanisms, manifestations, and treatment of COVID-19 pain. To do so, we should further study "Post-COVID-19 Pain Syndrome." Questions that are to be answered are: Is it a "Post-COVID 19 Pain Syndrome"? Persistent pain in patients suffered and recovered from COVID-19. The impact of COVID-19 infection on pain in chronic patients**.** What are the treatments for

Covid-19 pain? We need to develop new drugs targeted and specified for treatment of Covid-19 pain. What is the mechanism of Covid-19 pain? Why pain is becoming part of sequelae in Long COVID for some patients?

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Challenges in Current Chronic Pain Management

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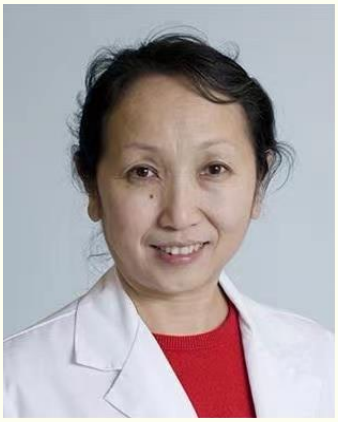

On July 16, 2020 the International Association for the Study of Pain (IASP) published a revised definition of pain: Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.[1] Chronic pain, a term that often refers to pain conditions that last more than three months,[2] is one of the most common reasons for patients to seek medical treatment.

Incidence and Prevalence

In the US, pain affects 100 million Americans.[3] About 25.3 million adults have daily chronic pain and 23.4 million adults experience a substantial level of pain.[4] The economic cost due to pain has been estimated at about $560–635 billion/year.[5] The incidence of chronic low back pain, neck pain, and arthritic pain may be as high as 29%, 15.7%, and 28%, respectively, in American adult populations.[6] The World Health Organization's 2010 Global Burden of Disease Study estimation indicates that low back pain is among the top ten clinical conditions affecting all age groups, particular in populations of 35 to 55 years old. The lifetime prevalence of low back pain is estimated at 60-70% in several countries.[7]

Clinical Challenges

Although advances have been made in pharmacological and interventional (e.g., nerve block) treatments for chronic pain, chronic pain remains inadequately controlled for many people. Moreover, side effects and complications of chronic pain treatments, such as addiction to opioid analgesics, kidney failure, or gastrointestinal bleeding due to long term use of NSAIDs, make it difficult to manage chronic pain conditions.

A. Medical Management and Opioid Crisis

Opioid therapy plays a significant role in current pain management. Opioid medications provide adequate pain control in most acute and some chronic pain conditions. However, a short or long-term opioid exposure could potentially lead to opioid addiction, misuse and abuse, or opioid diversion.[8]

For more than 20 years, opioid misuse, over-prescription, and unauthorized distribution (diversion) have resulted in a significant increase in opioid use disorders and accidental overdose death rate at alarming levels.[9-11] Around 6% of the US population (15–64 years old) reported some type of opioid abuse, and an estimated death of 115 US citizens per day due to opioid overdose was reported in 2015,[11] and over 66% of all overdose episodes in 2016 were opioid-related.[12]

Current efforts to address the opioid crisis have been made to identify potential associations between demographics (ethnicity, culture, gender, religion) and other factors with opioid accessibility, abuse, and overdose. Furthermore, numerous regulations and enhanced prescription drug monitoring programs have contributed to decreases in opioid prescriptions from 255 million prescriptions in 2012 to 191 million prescriptions in 2017, a 25% decrease.[13] Other measures would be valuable to manage the opioid crisis in the future, such as investigation of the nature of opioid use disorders, patient education, rehabilitation program, prescription drug monitoring program, as well as development of new opioid abuse-deterrent medications.

Non-opioid medications may be effective in reducing opioid dosages and minimizing opioid toxicity. Such medications include acetaminophen, NSAIDs, antidepressants, anticonvulsants, muscle relaxants, topical analgesics, and anxiolytics. However, these non-opioid medications are associated with their own risks with different mechanisms of action. These medications could be additive or synergistic when used in combination. However, a risk–benefit analysis must be performed prior to engaging in combination therapy in each individual patient.

Multiple complementary and integrative health approaches have been applied in managing chronic pain as well, including acupuncture, manipulative therapies, mind-body medicine, cognitive behavior therapy, etc. However, more data are still needed through innovative clinical research regarding the efficacy, side effects and other aspects of these treatment modalities. Thus, it is essential to continue to support clinical research in this field and give evidence-based recommendations to patients regarding each of these treatment modalities.

B. Interventional Procedures

Interventional pain procedures were initially introduced in the early 20th century and there have been substantial developments in diagnostic and therapeutic interventional techniques since then. Currently, interventional pain procedures are the second most commonly utilized technique in managing chronic pain. Multiple interventional techniques are evidence-based as well as cost-effective. They range from epidural steroid injection, facet joint injection and radiofrequency ablation, peripheral nerve block, joint injection, sympathetic nerve block, vertebral augmentation procedure, multiple neuromodulator techniques, intrathecal infusion pump, and finally regenerative therapies with interspinous prosthesis spacer devices.

There was an increased utilization of interventional pain procedures by 173.6% from 2000 to 2009. However, this trend has been reversed with a 6.7% decline, specifically epidural steroid injections, from 2009 to 2018.[14] Therefore, utilization of multiple interventional techniques in conjunction with other modalities such as physical therapy, home exercise programs and medical therapy may further improve chronic pain management.

C. Pain Management in Special Populations

Unique issues related to pediatric populations, adolescents, the patients with intellectual or developmental disability, the elderly, and pregnant women must be understood and addressed. These populations may have difficulty in communication about their pain which leads to inaccurate pain assessment, increased vulnerability for chronic pain, decreased effectiveness and increased risk of side effects from treatment, and decreased quality of life.

A proper guidance with evidence-based principles of managing these special patient populations must be provided so that multiple modalities of treatment as described above could be utilized to provide proper care for their chronic pain conditions.

D. Access to the Pain Specialty

Uneven access and quality of chronic pain management, including fragmented, inconsistent, and incomplete care, exist in America.[15] In addition, more pain specialists are needed in the field. According to the data from Association of American Medical Colleges on Physician Specialty Data Report in 2020 that reports the number of people per active physician, there are only 5,871 active pain physicians accounting for 56,453 people per active pain physician in 2019. It is necessary to train more pain physicians to provide proper care for the increased chronic pain population.

Challenges in Translational Pain Research

The current gap between basic science research and the development of new analgesics presents a serious challenge for the future of pain medicine. This is particularly difficult in the search for better treatment for comorbid chronic pain conditions because (1) animal 'pain' models do not simulate multidimensional clinical pain conditions; (2) animal behavioral testing does not assess subjective pain experience; (3) preclinical data provide little assurance regarding the direction of new analgesic development; and (4) clinical trials routinely use over-sanitized study populations and fail to capture the multidisciplinary consequences of comorbid chronic pain.[17] Therefore, a paradigm shift in translational pain research is necessary to transform the current focus on molecular switches of nociception to studying pain as a system-based integral response that includes psychosocial comorbidities. Translational pain research needs to involve a number of important areas including: 1) bridging the gap between pain research and clinical pain management; 2) developing objective pain-assessment tools; 3) analyzing current theories of pain mechanisms and their relevance to clinical pain; 4) exploring new tools for both preclinical and clinical pain research; and 5) coordinating research efforts among basic scientists, clinical investigators, and pain-medicine practitioners.[18]

In summary, chronic pain management is facing many challenges as discussed above. Enhancing translational pain research may help bridge the gap between basic science/clinical research and advancement of clinical treatment modalities to improve the effectiveness of chronic pain management.

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The role of Acupuncture in Pain Management

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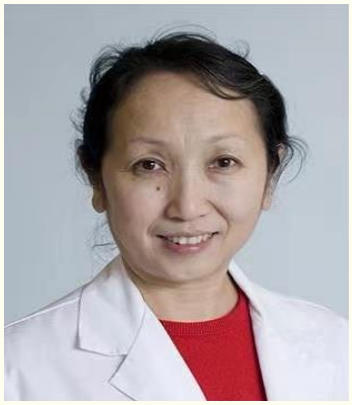

Chronic pain is a common medical problem. There are 25.3 million adults suffering from daily chronic pain in the United States.[1] Opioid therapy has been increasingly used to treat chronic pain conditions. However, the long-term use of opioids is complicated by its side effect, tolerance, dependence, abuse and opioid induced hyperalgesia. The increased complication and death due to over dose associated to the opioid use, has led the pain field to search for other medical treatment to manage chronic pain.

Recent data have shown that approximately 38 percent of U.S. adults and 12 percent of children use healthcare modalities that differ from conventional medicine for medical treatment or overall health maintenance.[2] In general, these non-conventional healthcare modalities are described in three terms: 1) *Complementary Medicine* refers to using a non-conventional modality in combination with conventional medicine; 2) *Alternative Medicine* refers to using a non-conventional modality in substitution of conventional medicine; and 3) more recently, *Integrative Medicine* has been used to describe the combined use of both conventional medicine and non-conventional modalities supported by at least some evidence of their safety and effectiveness. Complementary and integrative medicine include a variety of practices, which can be divided into five major categories based on the information provided by the National Center of Complementary and integrative Health (see Table 1). Currently, many medical schools in the United States have added a course of Integrative medicine.

Table 1. Categories of Complementary and Alternative Medicine

Alternative Medicine	Homeopathic medicine, Naturopathic medicine, Ayurveda, Traditional Chinese Medicine (herbs, acupuncture, massage)
Mind-body Interventions	Patient supporting groups, Cognitive-behavioral Therapy, Meditation, Mental healing, Art/Music/Dance Therapies
Bio-product-based Therapies	Herb products, Food/Vitamins, Dietary supplement, Natural products (e.g., shark cartilage)
Manipulative Therapies	Chiropractic manipulation, Osteopathic Manipulation, Massage
Energy- and Bio-field-based Therapies	Pulse field, Magnetic field, Alternating current, Direct current, Qi gong, Reiki, Therapeutic touch

Although originated from traditional Chinese medicine, acupuncture is perhaps one of the most commonly practiced therapies and is now used in nearly 100 countries.[3] It is also the most studied in both preclinical and clinical research of integrative medicine. As an ancient healing art, acupuncture has been the significant component of medical treatment in China for at least 3000 years. Over the last few decades, acupuncture has gained its popularity in the United States and is gradually being integrated into our healthcare system. In 1996, FDA classified acupuncture needles as medical equipment subject to the same standard of regulation for medical needles, syringes and surgical scalpels.[4] In 1997, National Institutes of Health (NIH) organized a Consensus Development Conference on Acupuncture, recognized that physicians, dentists, non-MD acupuncturists, and other practitioners have extensively practiced acupuncture. A major reason for patients to seek acupuncture treatment is a lower incidence of adverse effects than that of many drugs and commonly accepted medical procedures.[5]

Acupuncture for chronic pain

Chronic low back pain and neck pain are the leading cause of medical care and disabilities. National Health Statistics Reports describes back pain as the most common medical condition treated with complementary and integrative medicine.[2, 6] Whereas conventional treatments may have limited benefit in improving outcomes for some patients, acupuncture has been used as an additional option for the management of chronic low back and neck pain. One randomized multicenter study enrolled 1,162 patients with low back pain, acupuncture therapy improved their pain control for at least six months and significantly better than the conventional therapy.[7] In another large-scale clinical trial, 3,093 patients with low back pain were recruited and randomly assigned into acupuncture or conventional medical care. Back function (Hannover Functional Ability Questionnaire), pain, and quality of life were improved at three and six months in the acupuncture group.[8] The acupuncture treatment benefit was show in another randomized controlled multi-center trial to compare the effectiveness of acupuncture combined with routine care (1,880 subjects), with routine care alone (1,886 subjects), in patients with chronic neck pain. The results showed a significant improvement in neck pain and disability in the acupuncture plus routine care group.[9] A number of other pain conditions also have been treated with acupuncture as listed Table 2.[10]

Table 2 World Health Organization (WHO), 2002 data

Diseases, symptoms or conditions for which acupuncture has been shown to be effective	Diseases, symptoms or conditions for which the therapeutic effect of acupuncture remains to be determined
Low back pain	Radicular and pseudo radicular syndrome
Knee pain	Abdominal pain
Headache	Cancer pain
Neck pain	Fibromyalgia and fasciitis
Dental pain	Earache

Facial pain	Eye pain due to sub-conjunctiva injection
Postoperative pain	Labor pain
Rheumatoid arthritis	Pain due to thrombotic angiitis obliteran
Arthritis of shoulder	Pain due to endoscopic examination
Renal colic	Chronic prostatitis
Tennis elbow	Stiff neck
Sciatica	Acute spine pain
Sprain	Reflex sympathetic dystrophy
Cranio-mandibular dysfunction	Temporomandibular dysfunction
	Pruritus

Acupuncture for acute postoperative pain

Accumulating evidence suggests that acupuncture treatments are effective in improving postoperative pain and reducing opioid consumption. In a pragmatic study on postoperative pain management including 2,500 total hip and total knee replacement patients, adding acupuncture into an opioid regimen (72% of 2,500 cases) for postoperative pain management resulted in an average short-term pain reduction by 1.91 points (95% CI: 1.83, 1.99), a 45% reduction of baseline pain score without increase cost.[11] In a randomized controlled study (n=100) with 4 different groups (control, sham, low frequency or high frequency electro-acupuncture), the acupuncture effects on postoperative pain, opioid sparing, and opioid-related side effects were examined. The results showed that high frequency electro-acupuncture delayed the onset of analgesic request, reducing the total amount of morphine consumption by 61% in the first 24 hours postoperatively. The incidence of nausea and dizziness during this period was also significantly reduced in both electro-acupuncture groups as compared with the control and sham group.[12] Several randomized studies also support the notion that acupuncture or auricular acupuncture may be a useful adjunct for acute pain management, reduce opioid consumption and even reduce adjuvant medicine after hip or knee surgery, nephrectomy or even cardiac thoracic surgery.[13 - 18]

Conclusion

Despite the positive development regarding acupuncture as a tool in pain management, there are a number of challenges in clinical research of acupuncture therapy. (1) The scientific merits of acupuncture studies are, from time to time, limited by study design and non-standardized acupuncture practices. (2) There are difficulties in maintaining true blindness to patients in clinical studies. (3) Sham needling often elicits responses similar to real acupuncture treatment, making it difficult to interpret study outcomes. (4) Acupuncture treatment is highly individualized, varying from day to day and from one practitioner to another. With the advancement in research and improvement in insurance coverage, it is anticipated that more

patients will have access to acupuncture and other complementary medicine modalities as options of pain management. Acupuncture could play a growing and effective role in acute and chronic pain management as an opioid-sparing tool.

Take home message:

- Complementary and integrative medicine including acupuncture have gained its popularity for treating many medical conditions
- Complementary and integrative medicine include a variety of practices
- Accumulated data has supported the acupuncture treatment in many chronic pain conditions such as chronic low back pain and chronic neck pain in many large scale randomized clinical trials
- Randomized studies also support the notion that acupuncture also can be used to treat acute post-operative pain after different variety surgery
- There are a number of challenges in clinical research of acupuncture therapy
- Acupuncture could play a growing and effective role in acute and chronic pain management as an opioid-sparing tool.

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Prescribing opioids for chronic, non-malignant pain: an update since the CDC guidelines

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In 2016, the Centers for Disease Control (CDC) published recommendations for prescribing chronic opioid therapy for treatment of non-malignant pain.[1] The focus of its publication were twelve guidelines intended to provide guidance for primary care providers, who collectively prescribed the largest proportion of opioids. Some of these guidelines were generalizations, such as starting with non-opioid treatments, establishing treatment goals, and discussing the risks and benefits with patients. However, several of the guidelines set numeric thresholds for dose and duration of therapy: most notably, recommendation number 5 stated "Clinicians... should carefully reassess evidence of individual benefits and risks when increasing dosage to >50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to >90 MME/day or carefully justify a decision to titrate dosage to >90 MME/day."[1] For many health care providers, this seemed like a watershed moment. More than thirty state legislatures passed laws setting strict limits on the number of opioids that could be prescribed: Maine restricted opioid prescriptions to less than 100 MME/day,[2] Nevada less than 90 MME for initial prescriptions,[3] and Rhode Island passed a bill restricting treatment of acute pain to 30 MME or less.[4] Some physicians began tapering the daily usage of opioids to 90 MME for all their patients, and others refused to prescribe opioids altogether.[5-6] For perioperative physicians, including anesthesiologists, this coincided with a push to offer opioid-free surgery.[7]

Unfortunately, many patients who had been on long-term opioid therapy reacted unfavorably to these new changes, and a retraction within the medical field followed shortly afterwards. The authors of the CDC guidelines published an editorial in *The New England Journal of Medicine (NEJM)* in which they stated "some policies derived from [our] guideline have in fact been inconsistent with, and often go beyond, its recommendations…" With regards to recommendation #5 that clinicians avoid increasing doses above 90 MME, they wrote "this statement does not address or suggest discontinuation of opioids already prescribed at higher dosages, yet it has been used to justify abruptly stopping opioid prescriptions or coverage… An unintended consequence of expecting clinicians to mitigate risks of high-dose opioids is that rather than caring for patients receiving high doses, some clinicians may find it easier to refer or dismiss patients from care. Clinicians might universally stop prescribing opioids, even in situations in which the benefits might outweigh their risks."[8] Another letter signed by 300 medical experts, including three former White House drug czars from the Obama, Clinton, and Nixon administration, asked the CDC to clarify their guidelines to avoid the misapplication by

doctors or insurance companies.[9] And the American Society of Clinical Oncology and the American Society of Hematology wrote letters saying that despite the original guidelines specifically stating that they did not apply to patients undergoing active treatment for cancer or sickle cell disease, patients with those ailments were facing roadblocks from insurance companies or others with obtaining the medications as prescribed.[10] The rapid shift in attitude is not surprising when seen in the context of the history of opioid prescribing in the United States: there has always been a dearth of evidence to prove any long-term benefit of chronic opioid use, resulting in a cyclical pattern of opioid prescribing that has been influenced in large part by consensus statements from a variety of medical societies and government entities.[11]

1912-1980: Government regulation from the International Opium Convention to the Controlled Substances Act

In the decades leading up to 1980, United States federal law was one of the few guidelines for providers prescribing opioids for pain. Much of the extant law during that period aimed to mitigate the risk of addiction to illicit opioids, which had been well-documented since the discovery of opium. Opium cultivation from the poppy plant has been traced back to the Sumerians in Mesopotamia in 3400 BC.[12] Morphine was extracted from opium in 1803 by a German pharmacist.[13] Diacetylmorphine (or heroin) was synthesized in 1874 by an English chemist, and was produced commercially by Bayer in 1898, initially as a less addictive alternative to morphine.[14] In 1912, the US signed the first international drug control treaty, named the International Opium Convention, along with 11 other countries including China and Russia. The treaty said the countries would "use their best endeavors to control, or to cause to be controlled, all persons manufacturing, importing, selling, distributing, and exporting morphine, cocaine, and their respective salts, as well as the buildings in which these persons carry such an industry or trade."[15] Within US law, Congress then passed the Harrison Narcotics Drug Act in 1914, which regulated the dispensing of opioids by physicians, dentists, and veterinarians.[16] Oxycodone was first synthesized in 1916,[17] and by the 1960's had become a prevalent drug of abuse. In response, President Richard Nixon launched the "War on Drugs" in 1971 and Congress subsequently passed the Controlled Substances Act, [18] which made heroin illegal and classified other strong opioids as Schedule 2 medications.

1980-2009: A letter to the editor and the Decade of Pain Control

On January 10, 1980, *NEJM* published a letter to the editor from Dr. Hershel Jick, a professor of medicine at Boston University who had created a hospital database to track the effects of all kinds of drugs. His database included 11,882 hospitalized patients who received at least one "narcotic preparation", and with a graduate student named Jane Porter, he wrote that only four developed "reasonably well documented addiction."[19] Although he did not intend it at the time, this simple paragraph-long letter became the lynchpin for the argument that opioids were not addictive if used for medical purposes and even became a part of medical parlance as simply "Porter and Jick."

During the remainder of the 1980's, other experts in the field of pain medicine supported the idea that opioids were not addictive.[20-21] Furthermore, many felt that pain -- in particular cancer-related pain, but also non-malignant pain -- was being undertreated as a result of stigma associated with opioid prescribing. In 1991, *Annals of Internal Medicine* published an editorial in which the author argued that pain should be a "visible" part of the patient's record, like how

vital signs were in a prominent part of the patient's chart.[22] The American Pain Society (APS) cited this editorial in its quality assurance standards,[23] which some governing bodies (such as the California state legislature) took to mean that pain should be measured at the same intervals as temperature, heart rate, respiratory rate, and blood pressure, thus creating the "fifth vital sign".[24]

The first prominent systematic review of the use of opioids for chronic non-malignant pain came from the Department of Defense (DOD) and Veterans Affairs (VA) Administration in 2003. Congress had earlier declared the ten years beginning on January 1, 2001, as the "Decade of Pain Control and Research."[25] The DOD/VA review gave a grade A recommendation for initiating an opioid trial for nociceptive or neuropathic pain and titrating to an adequate level of analgesia.[26] This recommendation was made despite the absence of any randomized controlled trials of opioid use lasting longer than 6 months. As expected, the end of the decade of pain control saw the number of opioid prescriptions nearly triple from 1991 to 2011.[27] However, the number of deaths attributed to prescription painkillers also rose, and by 2013, nearly 20,000 deaths in the United States were attributed to overdose from prescription opioids.[28]

2009-2016: More systematic reviews

Several large systematic reviews of opioid use followed the DOD/VA study, including ones by the APS and the American Academy of Pain Management (AAPM) in 2009 [29] and by the Agency for Healthcare Research and Quality (AHRQ) in 2014.[30] Both studies looked at multiple questions about the now well-documented risks of opioid use for the treatment of non-malignant pain and tried to identify studies addressing its efficacy. In 2005, a trial of patients with low back pain taking fentanyl transdermal versus oral morphine was the first randomized trial of opioid therapy lasting greater than 12 months; what was most notable about the study was that 51% of study participants did not remain on their assigned therapy.[31] Ultimately, the authors found a 1-2 point improvement on a 10 point scale when opioids were used. There were still no randomized controlled trials comparing opioid to non-opioid therapy lasting longer than 12 months when the CDC guidelines were published in 2016.

The CDC guidelines were the result of a systematic review of the literature that included the APS/AAPM and AHRQ reviews that came before. Like the two previous reviews, the authors found insufficient evidence supporting the efficacy of long-term opioid therapy. They were also unable to predict which patients or pain symptoms would be most likely to respond to opioid medications. When it came to their twelve recommendations, the authors acknowledged that the first 11 recommendations (including those about the appropriate dose and duration of opioid medication) were based on type 3 or 4 evidence, meaning observational studies or randomized controlled trials with notable limitations.[1]

2016-Present: After the CDC guidelines

In 2018, the *Journal of the American Medical Association* published the first randomized controlled trial lasting one year, comparing opioids to non-opioids for 240 VA patients with moderate to severe chronic low back pain or hip/knee osteoarthritis pain.[32] The authors found no difference in pain scores, which went down by a little less than 2 out of 10 in both groups, as well as no difference in pain-related function scores. Three years later, the same journal published a retrospective cohort study of patients who had been on a high-dose, long-term opioid regimen, some who had been forced to taper off. They found an adjusted incidence rate of 9.3

overdose events per 100 person-years in tapered periods vs 5.5 events per 100 person-years in non-tapered periods.[33]

While most pain experts continue to acknowledge that long-term opioid use is not the solution to chronic pain management, the focus has shifted away from eliminating opioids altogether, but instead towards promoting other methods of analgesia that may be less risky. In their 2019 *NEJM* editorial, the authors of the CDC guideline concluded by saying "appropriate implementation of the guideline includes maximizing use of physical, psychological, and multimodal pain treatments. However, these therapies have not been used, available, or reimbursed sufficiently. The CDC has supported research to better define the evidence and coverage gaps for nonopioid pain treatments and has articulated the need to improve insurance coverage. Efforts to support more judicious opioid use will become more successful as effective non opioid treatments are increasingly available and used."[8] Within perioperative medicine, anesthesiologists scaled back from the push for "opioid-free anesthesia" and re-framed the administration of a balanced anesthetic as "opioid-sparing."[34]

In 2016, the Department of Health and Human Services, in conjunction with the DOD and the VA formed an Inter-Agency Task Force. The task force included pain experts both in and out of government. Together, they reviewed scientific literature and heard about 9000 public comments. In 2019, the task force published its recommendations,[35] which focused on a biopsychosocial model of care with five prongs, placing equal weight on medications, restorative therapies (such as physical/occupational therapy), interventional approaches, behavioral approaches, and complementary/integrative health. Regarding opioid prescribing, the task force pushed back against what it considered to be the misguided implementation of the CDC guidelines by state governments, insurance companies, and physicians. In its introduction, the task force wrote that it recognized the utility of the CDC guidelines and its "contribution to mitigating unnecessary opioid exposure and the adverse outcomes associated with opioids. It also recognizes unintended consequences that have resulted following the release of the guidelines in 2016, which are due in part to misapplication or misinterpretation of the guideline, including forced tapers and patient abandonment." They later go on to say, "Clinical practice guidelines for best practices that only promote and prioritize minimizing opioid administration run the risk of undertreating pain, especially when the cause of the pain is uncertain or cannot be reduced through non-opioid approaches... Although effective for moderate to severe acute pain, the effectiveness of opioids beyond three months requires more evidence." However, they were clear in not establishing a ceiling dose, saying "The idea of a ceiling dose of opioids has been recommended, but establishing such a ceiling is difficult, and the precise level for such a ceiling has not been established."[35]

The recommendations from the Inter-Agency Task Force will not be the last expert opinion we hear on this issue. The CDC has announced that it plans to respond to the concerns raised by multiple medical societies -- including the American Medical Association – and to publish revised guidelines, likely in early 2022.[36] Unfortunately, they do not have very many new clinical trials to inform their new guidelines. Just as in the past, they will have to rely on a disparate consensus of physicians.

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Ketamine and Its Use as an Infusion for Lasting Effects in the Outpatient Treatment of Chronic Pain: A Narrative Review Article

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Background

The dissociative anesthetic, Ketamine, is one of the few anesthetics that alone can provide all the components of a general anesthetic: analgesia, amnesia, anxiolysis, anesthesia (awareness), and muscle relaxation. In addition, it is able to maintain airway reflexes. These unique properties lend to its many uses, such as a general anesthetic, induction agent, procedural sedative, infusion for acute pain, chronic pain, and depression. This article will overview Ketamine and then delve into evidence for its lasting effects when used as an infusion to treat chronic pain.

Side Effects

Cardiopulmonary

Ketamine can increase blood pressure, heart rate, cardiac output, and myocardial oxygen demand by causing a systemic release of catecholamine, vagal nerve inhibition, and norepinephrine reuptake inhibition.[1] For this, the use of ketamine may want to be avoided in a variety of situations. It can cause ischemia in high-risk patients, such as those with coronary artery disease. In surgeries where increases in blood pressure can be detrimental, such as aneurysm clipping, ketamine may be avoided. On the other hand, Ketamine's catecholamine release can have positive influences in patients with bronchospasm by causing bronchodilation. It can also be helpful on induction in patients that need blood pressure maintained, however ketamine is a direct myocardial depressant. This cardiac depression is generally negated by the catecholamine release, but with catecholamine depletion, such as that seen with prolonged shock, cardiac collapse could still result.

Psychiatric

Bolus dosing and infusions have been associated with psychomimetic effects, such as hallucinations, delirium, out of body sensation. Thus, consider avoiding the use of ketamine in patients with delirium, PTSD, or prior negative experiences. It is patient dependent whether psychomimetic effects are taken negatively or positively, and there does not seem to be a dose response relationship on how patients perceive these effects as positive, negative, or tolerable.[2, 3]

Sialogogue

Ketamine causes increased oral secretions that can be obstructive for airway procedures, but this effect can be minimized with anticholinergics like glycopyrrolate.

Nausea and Vomiting

There is confounding evidence on whether Ketamine increases or decreases nausea and vomiting. In a large number of studies using ketamine infusions, patients in the ketamine group had increased incidences of nausea and vomiting. However, it may lend to decreased nausea and vomiting in the operative setting due to decreased opioid use.[4]

Cystitis

Ketamine has been associated with the development of chronic cystitis, although nearly all reports have been in abusers. In one study, 9 abusers presented with symptoms of painful hematuria, dysuria, urgency, frequency, and post micturition pain. Biopsies showed ulcerative cystitis with an eosinophilic infiltrate. The mainstay of treatment is to stop Ketamine. Anticholinergics and mucosal protective agents, such as pentosan polysulfate which supplements the glycosaminoglycan layer of the bladder, can be helpful. Antibiotics and steroids did not show improvement. While cessation of ketamine helped, some patient continued to have lifelong symptoms.[4]

Hepatotoxicity

Impacts on the liver have been seen in studies on abusers and incidentally in clinical trials. In one assessment of 297 chronic ketamine abusers, 9.8% were found to have cholestatic pathology, including common bile duct dilation, microscopic bile duct injury, and even significant liver fibrosis. Of note, all these were also positive for urinary tract dysfunction.[5] Case reports came out of a study on ketamine's use for type 1 complex regional pain syndromes (CRPS) when 3 of 13 patients developed liver enzymes greater than three times the upper limit of normal. The study was designed to give an infusion twice, over 5 days 16 days apart, titrated up to 0/10 pain. The patients did receive high doses; one received 1.3 grams and another 800 mg over 3 days which may have contributed to the spike in liver enzymes.[6] However, this is in contrast to a major study done on 60 patients getting a 100 hour infusion, up to 2.5 grams, where liver enzymes remained unaffected in all patients.[7] There does seem to be some association with higher dose and liver injury, but evidence is confounding, and studies have yet to determine outcomes for long term use in the medical setting.

Other Side Effects

Consideration should be given when administering ketamine may be avoided in patients to with abuse potential because of its hallucinogenic, dissociative, and euphoric properties.

Its effect on catecholamine caution its use in patients with pheochromocytoma and hyperthyroidism.

Ketamine is a pregnancy class B drug. It is often used in cesarean sections as a pain adjunct to maintain respirations during an incomplete neuraxial anesthetic, but is used less during the developmental stages of pregnancy.

Pharmacology

Pharmacokinetics

Ketamine is metabolized by the cytochrome p450 enzymes in the liver, primarily CYP2B6 and CYP3A4. The activity of ketamine can therefore be influenced by other medications. Medications such as macrolides and azoles that inhibit cytochrome can prolong its duration of action. Alternatively, anti-seizure medications (e.g. phenytoin) often induce cytochrome enzymes and result in decreasing ketamine's duration. Metabolites are renally excreted, the primary one being Norketamine which is 1/3 to 1/5 weaker.[8]

Pharmacodynamics

Ketamine is active at many sites but the primary target, the NMDA (N-methyl-D-aspartate) receptor, opioid (mu>kappa>sigma), Dopamine D2, muscarinic acetylcholine, innate repair, and HCN1 (hyperpolarization-activated cyclic nucleotide-gated channel 1) receptors are also effected.[9] Ketamine's action on the HCN1 receptor blocks signal transmission by blocking Na-K channels. The innate repair receptor is similar to erythropoietin and beta common receptor which activates anti-inflammatory and tissue repair pathways. The NMDA receptor is a ligand gated channel primarily activated by glutamate, but also relies on glycine binding by unguided diffusion. Blocking the above channels can decrease signal transmission and inflammation.

Central Sensitization

Central sensitization happens when the intensity of pain is out of proportion to tissue damage due to aberrant pain processing. Blocking NMDA receptors blocks excitatory signals from damaged peripheral sites from reaching the brain. Thus ketamine can prevent central sensitization and windup.[9] There are no human studies that confirm quantitative changes in sensation in relation to central sensitization. But there is a mice study that shows ketamine works better in chronic stages of CRPS (when central mechanisms predominate) than in acute stages (when peripheral mechanisms predominate). In this study mice were given femur fractures. In the acute stage they had increased limb temperature, edema, and nociceptive sensitization. These symptoms were not reduced by ketamine (though pain likely was). During the chronic phase of healing, the mice were given ketamine, resulting in reduced nociceptive sensitization that persisted beyond completion of the infusion. These mice also had improved motor function at 18 weeks. This supports ketamine's reduction on central sensitization.[10]

PTSD

Ketamine blocks excitatory signals in other parts of the brain, including signals to the hippocampus, amygdala, and prefrontal cortex. These areas of the brain are all intertwined in traumatic experiences. The hippocampus is involved in memory, the amygdala is a center for emotion and instinct, and the prefrontal cortex regulates these emotions and impulses associated with memories. Inhibiting transmission can help inhibit recurrence of a traumatic experience. On the other hand, it is important to keep in mind that ketamine can cause an exacerbation of PTSD in the acute setting, especially if a patient received the drug during a traumatic experience which is common for wounded warriors.

Enantiomers

Both the R (-) and S (+) enantiomers of ketamine are available. The S-enantiomer is now

FDA approved and available for intranasal administration. The S-enantiomer is generally thought to have stronger analgesic and hypnotic properties but less locomotor activity, fewer side effects, but greater increases in blood pressure and heart rate,[11] whereas the R-enantiomer may have more sustained antidepressant effects.[12, 13] Evidence to support these claims is inconclusive and contradictory however. A study on the nociceptive withdrawal reflex of standing ponies tried to elucidate which enantiomer may have better analgesic properties. One study group received a racemic bolus and then infusion, while the other group got an S-ketamine bolus and then infusion. The S-ketamine group received half the dose, however the plasma concentration of S-ketamine in both groups was the same. The nociceptive withdrawal reflex was only depressed in the racemic group. This could mean that ponies have a different response to R and S-ketamine that R-ketamine are more efficacious in pain, or that R and S ketamine are additive/synergistic in efficacy. Regardless, it does support that R-ketamine is active as an analgesic.[12]

Evidence

Neuropathic pain is defined as pain caused by a lesion of the somatosensory nervous system, central or peripheral. It is often described as burning, electric, shooting, and associated with hyperalgesia and allodynia. It can be associated with reduced pain thresholds or a heightened response to nociceptive input, also referred to as central sensitization. This section will cover the evidence for ketamine's use for a variety of neuropathic pain disorders, primarily focusing on blinded randomized controlled trials (RCTs). A large review article, published in 2018 called the Consensus Guidelines, reviewed many of these trials. It gauged the evidence and gave graded recommendations on using ketamine and will be referenced below.[14]

Traumatic Spinal Cord Injury

Weak Evidence, Grade C Recommendation1[4]

There were 3 double blind randomized controlled trials (RCTs) that showed significant reduction in pain during infusion.[15-17] Only one of the studies followed patients long term. In this study by Amr, one group received a ketamine infusion of 80 mg over 5 hours per day for one week plus gabapentin, while another received placebo plus gabapentin. There was a significant difference in pain at the 2 week mark ($p<.001$), but not at the 3 and 4 week mark.[17] There was wide dosing variability amongst the studies, from about 0.4mg/kg for 17 minutes to 80mg a day for 5 days, making it difficult to pinpoint an effective dose.

Two other studies of note were done under the author Amr. These studies looked at epidural ketamine for chronic spine related pain. In one study, 40 patients with post spinal cord injury related pain were given a onetime epidural injection of 0.2mg/kg of ketamine and had significant relief for 30 days.[18] Another study involving 200 patients gave epidural ketamine injections for lumbar radicular pain. One group received 30 mg ketamine, bupivacaine, and steroid, while the second group received placebo, bupivacaine, and steroid. There was significant pain relief up to one year.[19] These studies indicate a potential use for epidurally administered ketamine.

Phantom Limb Pain

Weak Evidence, Grade D Recommendation1[4]

Again there is little evidence with long term follow-up. There were two RCTs that showed significant pain relief during infusion.[20, 21] Only one of the studies followed patients after

infusion, and found a significant difference in pain at 48 hours, but did not follow further. This study gave a 0.4 mg/kg bolus.[20] The other study gave 0.1 mg/kg followed by a 7 mg/kg/hr infusion and found significant relief during infusion.[21]

Post Herpetic Neuralgia

Weak Evidence, Grade D Recommendation1[4]

There was only one trial that was double blind randomized. It involved 8 patients that either received morphine at 0.075 mg/kg plus ketamine at 0.15 mg/kg or morphine plus saline. Allodynia and wind up pain were significantly better in the groups that also received ketamine at 15 and 45 minutes after infusion.[22] Due to the limited amount of trials, it is difficult to say whether ketamine will provide long-term relief for post herpetic neuralgia. This does however support there is an NMDA mechanism that ketamine could help.

Fibromyalgia

Weak Evidence, Grade D Recommendation1[4]

There are few trials on fibromyalgia that followed patient's long-term symptoms and one of the few that did not show long-term relief. Four double blind RCTs found significant improvements in pain during and immediately following infusion. Dosing ranged from 0.3 mg/kg to 0.5 mg/kg over 10 to 30 minutes.[23-26] In the study with long term follow-up 24 patients received S-ketamine at 0.5mg/kg or 5 mg midazolam. They had immediate relief, but no significant relief from 2.5 hours to 8 weeks.[26]

Ischemic Pain from Severe Peripheral Vascular Disease

Weak Evidence, Grade D Recommendation1[4]

There were two double blind RCTs, one in which ketamine was compared with morphine showing no significant difference,[27] and another where ketamine was compared with placebo resulting in significant pain relief at day 1 and 5. In the latter study 35 patients received morphine plus ketamine 0.6 mg/kg over four hours, or morphine and placebo.[28] This supports ketamine as a good pain adjunct, as it is known for its analgesic properties, but does not necessarily support its impact on central mechanisms to provide lasting relief for ischemic pain patients.

Migraine Headache

Weak Evidence, Grade D Recommendation1[4]

One two-part double blind RCT of 17 patients found significant improvements in pain. In the first part 17 patients with acute migraine received 80 mcg/kg subcutaneous ketamine. In the second part 17 patients with refractory migraine received 80 mcg/kg subcutaneous ketamine three times a day versus placebo for three weeks. Both groups had significant relief, supporting ketamine's use as abortive and prophylactic therapy for migraines.[29]

There is otherwise conflicting evidence for ketamine as abortive migraine therapy, especially in the emergency department setting.

Complex Regional Pain Syndrome

Moderate Evidence, Grade B Recommendation1[4]

Complex Regional Pain Syndrome has the most evidence to support ketamine's use. There are two compelling double blind RCTs involving 79 patients total that compared ketamine and saline. In the first trial, Sigtermans and colleagues studied S-ketamine with an average infusion time of 22 mg/hr for 4.2 days versus placebo. They found significant improvements in pain scores at weeks 1-11, but not week 12. This study involved 60 patients, 48 female, with type 1 CRPS that received their infusions as inpatients. The infusion was started at approximately 5 mg/hr and titrated every 2 hours during the daytime and every 8 hours at night time based on pain score and side effects to a max dose of 30 mg/hr for 5 days. Weekly liver function tests and blood pressure measurements remained unaffected. Ketamine group patients experienced more nausea and vomiting and psychomimetic effects. In two of the patients, on days 3 and 4 respectively, the infusion was terminated due to an "intense feeling of high," but their results were still included in the pain analysis. There was significant pain improvement through weeks 1-11, with the most at week one ($P<0.001$), as can be seen in figure 1. Of note, although there was significant pain relief, there was no functional improvement found. Figure 2 shows the plasma concentration of ketamine during and immediately following infusion. This demonstrates that the lasting pain relief was not a direct result of ketamine in the plasma, since levels quickly dropped off. It also gives a reference for future studies or treatments that could aim to reproduce similar plasma levels.[7]

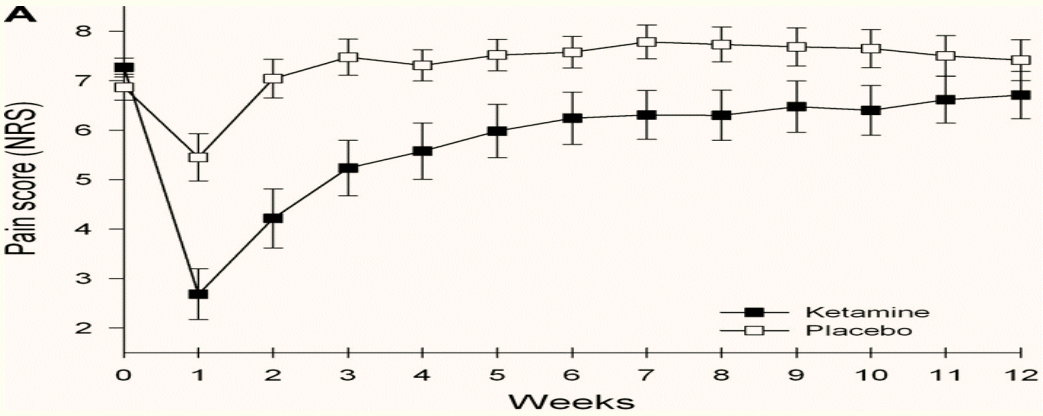

Figure 1**:** Pain scores in Ketamine treatment group versus placebo group over 12 weeks.[7]

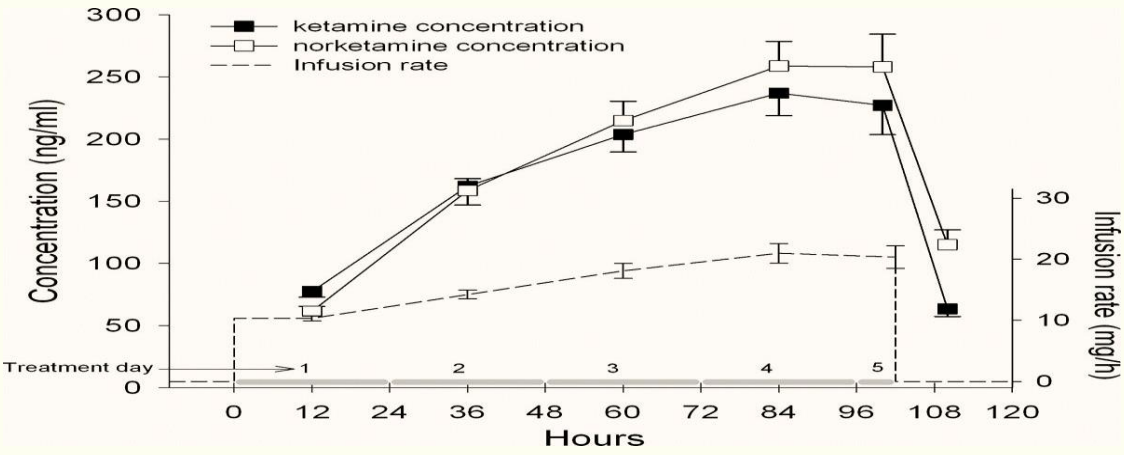

Figure 2: Ketamine infusion rate compared with plasma concentration, showing rapid decline in plasma concentration after infusion termination.[7]

In the second notable study Schwartzman and colleagues administered racemic ketamine vs placebo and found significant differences in pain through 12 weeks. It involved 19 patients in an outpatient setting. All patients received midazolam and clonidine for side-effects. Infusions lasted for 4 hours a day for 10 days. On day one patients received 50% of the max dose, on day two they received 75% of the max dose, and from day three and on, they received the max dose of .35 mg/kg/hr (approximately 100 mg over 4 hours). 4/9 patients in the ketamine group had complaints of nausea, headache, tiredness, and dysphoria and 2/10 did in the placebo group. Figure 3 shows the progression of pain relief in the two groups, with significant relief seen for the full 12 weeks ($p<.05$). Interestingly, the largest difference in pain score was after weeks 3-4, compared with week 1 in the study by Sigterman. Again, there was no increase in activity level, but there were fewer night time awakenings in the ketamine group. This study may have had increased power, except that it was stopped at the halfway point when the authors achieved the significance they wanted. They concluded that with twice the dosing ketamine may have more significant pain improvements and planned to follow up on this effect.[30]

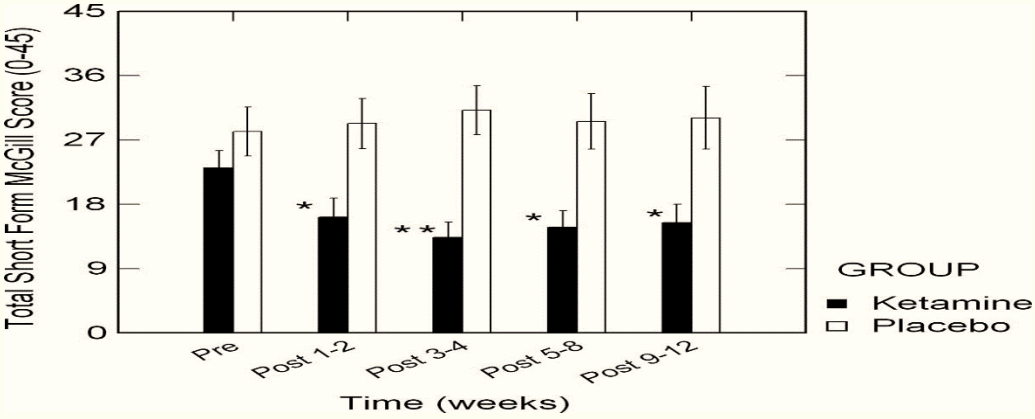

Figure 3: Differences in pain score on McGill questionnaire between ketamine and placebo groups at different intervals (pretreatment was at least two weeks before treatment).[30]

Recent Research on Ketamine for Neuropathic Pain

A recent randomized, double-blind, crossover study was published in *Anesthesiology* in July 2020 that compared ketamine, magnesium plus ketamine, and placebo in 20 patients with chronic neuropathic pain. All patients received all three infusions, in random order, 35 days apart. Their pain scores were recorded daily and the primary outcome was area under the curve for the 35 days after each infusion. Ketamine was given at 0.5 mg/kg and Magnesium at 3 grams. There was no significant difference found for any of the three groups ($P=0.296$). Figure 4 shows the average pain score over the 35 days post each infusion for each of the 20 patients. It is important to note that the patients in this trial had a variety of neuropathic pain types, including post-surgery, radiculopathy, posttraumatic, post-diabetic, and post-chemotherapy. None of the pain types were specifically CRPS, which prior evidence most supports treatment for. Ketamine was also given in low dose when compared with the before mentioned trials by Sigtermans and Schwartzman. Both of these points likely contributed to the results of this trial not showing ketamine infusion benefits for neuropathic pain.[31]

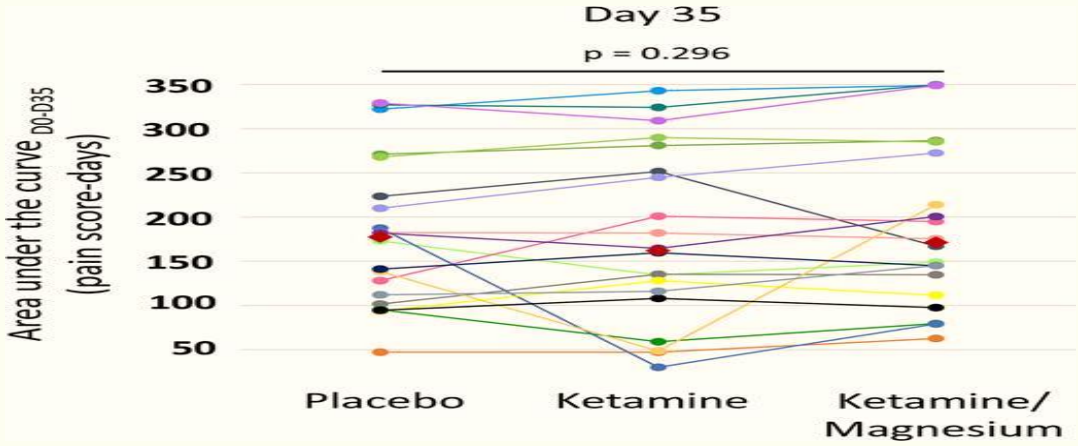

Figure 4: Average pain score over the 35 days post each infusion for each of the 20 patients. Each color represents a different patient.[31]

Dosing Guidelines

Determining a proper dosing regimen for ketamine infusions is difficult due to the wide range of total doses and infusion/bolus regimens reported in studies. In the aforementioned studies dosing has ranged from a low dose one time bolus of 0.4 mg/kg [23] to a high dose infusion over days at 7 mg/kg/hr.[32] In addition, there are few studies on dose response relationships that compare different doses of ketamine, instead of comparing ketamine versus placebo. One study on refractory neuropathic pain in cancer patients already on morphine, found that there was more relief with higher dosing, but also more side effects, and pain relief was only measured for up to 3 hours.[33] Still, there are some papers that have attempted to give cursory recommendations on dosing.

Maher and colleagues concluded that evidence supports a dose response relationship. In this literature review they provide a table of many of the large studies with dosing regimens and pain outcomes. They claim level 2 evidence supports that higher dosing over longer periods of time with more frequent administration is more effective, secondly rate is irrelevant, and lastly regardless of dosing, side-effects are common, so adjunct medication like clonidine and midazolam are helpful.[34]

Noppers and colleagues concluded infusions less than 2 hours were unlikely to provide relief after 48 hours. Infusions over 10 hours had a 95% chance of significant pain relief after 48 hours, and infusions over 30 hours had nearly a 99% chance.[26] The Consensus Guidelines take a much more reserved approach, recommending to start with a single outpatient infusion of 80 mg lasting more than 2 hours and reassess before initiating further treatment (grade C recommendation).[14]

Conclusions

Based on the evidence, much higher dosing is likely needed for long-term relief from chronic pain, as compared with depression (which is often 0.5 mg/kg over 40 minutes). This may make it less suitable for the outpatient setting, although the study by Schwartzman and colleagues was successful as high dose outpatient treatment.[29] These studies can be difficult to blind since ketamine has such profound psychomimetic effects. Patients receiving adjunct medications, such as midazolam and clonidine, may help with this by decreasing side-effects and giving the

placebo group a reason to be altered. Evidence best supports ketamine's use for CRPS, but further research is needed to better define proper dosing, and to discover if ketamine may be beneficial for other pain syndromes. It will also be important to monitor long term side effects. As patients are given repetitive ketamine treatments over time, bladder and liver injury may become more apparent.

Chronic pain creates a socioeconomic burden. It is a leading cause of disability in the US. A 2010 report stated that 1 in 3 Americans are affected by chronic pain, costing approximately $600 billion dollars a year, and the burden is similar in Europe. Although the two large trials mentioned for CRPS did not reveal improvements in activity, it is possible that when combined with physical therapy and behavioral therapy, ketamine infusions could lead to significant functional improvement over time.

Depression is also a leading cause of disability in the US.[35] Since ketamine has efficacy in treating depression, treating pain may result in dual treatment because the two conditions often coincide. As more studies are done and providers continue to use ketamine in its off label uses we will develop a better understanding of whether it is a reliable treatment modality.

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多学科团队合作和中国区域疼痛科发展
--广东慢性疼痛多学科专家交流平台发展

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2007 年 6 月，国家卫生部正式发文, 规定在国内二级以上医院成立疼痛科的 10 多年来，中国疼痛科进入快速发展期，除了自身努力外，兄弟学科的理解和支持也是关键之一。许多年前，中华医学会疼痛学会终身荣誉主任委员韩济生院士就一直提倡建立多学科联盟，中国疼痛科医师面对大量的慢性疼痛病人就已经意识到：要想打好抗痛的狙击战，必需要建立强大的多学科团队，共同研究、治疗慢性疼痛，近十多年来我的团队在临床实践中努力践行多学科团队合作（Multi-Disciplinary Team，MDT）的理念和实施途径。进一步推动了区域疼痛科的健康发展。

一 、多学科团队合作与疼痛科的发展

长期以来，中国大多数三甲医院临床科室都建立有互请会诊制度，随着日益增加的难治性病例，多学科团队（Multi-Disciplinary Team，MDT）合作、会诊已经逐渐成为疑难病临床医疗或护理的方向之一。[1-3]中国疼痛科作为一个新型临床学科，逐渐成长，规模壮大，技术逐渐规范化。但是全疼痛人群众多（30-35%），慢性疼痛病人花费巨大，PAIN 杂志（2019）资料报道指出，全球每年为此花费最高的国家达 $ 6000 亿。[4-6]年轻的疼痛科面对及处理如此大量的病人存在许多困难，借助成熟的兄弟学科成长经验不仅有益于提高临床医疗质量，也能够帮助疼痛科进入良性发展道路，所以慢性疼痛 MDT 交流平台对于疼痛科发展过程有着非凡的意义。

1. 疼痛病宣传、科普作用：刚刚成立的疼痛科，需要社会和媒体的熟悉和了解，兄弟学科也要知道疼痛科的业务诊疗范围，特别是在基层医院疼痛科可能引起疼痛诊疗相关科室的误解和抵制。通过 MDT 联谊活动，除了宣传疼痛科理念外，可以使兄弟学科了解疼痛科工作范围，逐步消除一些误解，促进疼痛科融入多学科临床。

2. 促进疼痛科加强诊疗基本功和规范化诊疗：一个合格的疼痛科医师需要具备神经科的检查技术、骨科的诊断技术、麻醉科的穿刺技术、放射科影像技术和心理科的心理疏导技巧的综合技术。[7]多学科专家的临床诊疗经验和技术能够帮助疼痛科进一步加强自身建设和诊疗水平提高。特别有助于促进疼痛诊疗规范化程序建立、提高疼痛科临床医疗质量工作。

3. 新技术和信息交流：通过多学科交流平台，多学科专家相互交流对慢性疼痛的理解和研究进展，能够帮助疼痛科从不同的角度加深对慢性疼痛的认识，合理使用常用药物。同时疼痛科把具有疼痛科特色的微创介入经验和技术介绍给兄弟学科，给他们在临床上处理一些慢性疼痛病增加新思路和新方法。

4. 帮助兄弟学科处理难治性疼痛病：这是广东慢性疼痛 MDT 交流平台建立 5 年来最有价值的亮点。通过交流平台，许多兄弟学科遇到的难治性疼痛病：包括脊柱手术后慢性疼痛、周围神经痛、截瘫后和截肢后神经痛、糖尿病足疼痛、化疗后疼痛和难治性肿瘤疼痛等病例都是疼痛科提供了及时、有效的帮助，通过疼痛科的介绍，相关学科也学习了这些难治性疼痛病的常规诊疗和管理，得到多学科专家的欢迎和赞赏，也使他们加深了对本单位疼痛科的理解和支持，收到了多赢的效果。

二、 广东慢性疼痛 MDT 交流平台的筹备过程

10 年前，王家双教授主持广州市疼痛学期间就着手考虑如何尝试建立慢性疼痛区域多学科协作交流。怎样开始在广州地区工作繁忙的各大医院间建立临床 MDT 交流，以促进疼痛科发展和提高临床诊疗水平一直是王家双教授团队面临的主要问题。但是这是一项极具挑战性的事业，需要把各大医院临床疼痛诊疗相关学科组织在一起谈何容易。2014 年底刚刚从行政岗位退下后，有了一些空余时间，他开始探索如何实施 MDT，进一步促进和加强广东地区的多学科慢性疼痛诊疗和研究途径和方式。

基于 20 多年在各级医学会和参与广州市政协工作期间与多学科专家建立的交流、联系和友谊的基础上，王家双教授首先找到自己比较熟悉的广州地区对慢性疼痛诊疗有兴趣的六个专科的专家：神经内科（广东省人民医院周主任、广州医学院附二院高主任）、骨科（南方医大珠江医院陈主任），康复科（中山大学附二院马主任，中山大学附三院胡主任）和广东省医院疼痛科王主任等商量，征求他们的意见，由于大家对于慢性疼痛都有共同的兴趣，也面临大量的难治性疼痛病和许多慢性疼痛诊疗的实际问题，大家意见基本一致，认为非常有必要建立一个跨学科 MDT 平台交流信息和治疗方法。

经过半年多的准备，2015 年国庆节后的金秋十月中旬，秋高气爽，正值 2015 世界疼痛日和中国疼痛周活动期间，2015-10-22 下午，在广州珠江新城华普广场—王家双教授工作室，中山大学附一院麻醉科陈秉学教授领头和来自广州地区 12 家大医院的神经科、康复科、骨科、麻醉科和疼痛科的近 20 位多学科专家聚集一堂开始讨论主题。作为牵头人，王家双教授提出了组建广东慢性疼痛 MDT 的思路和具体计划，提供大家讨论。结果超出他的预想，参加会议的多学科专家们表现出高度兴趣，异口同声表示计划可行，一致赞成并积极参与。热情高涨的到会专家各抒己见，纷纷提出建设性的意见，一直持续到晚间。经过协商、讨论一致同意成立 “广东慢性疼痛 MDT 专家协作组暨交流平台”及微信群。大家一致表态要用实际行动积极推动广东的慢性疼痛和顽固性神经痛临床工作的合作、进步和慢性疼痛科学普及宣传工作。

广东慢性疼痛多学科交流平台启动仪式留影

三 慢性疼痛 MDT 交流平台的趣味主题

神经病理性疼痛（简称神经痛）是临床许多学科面临的难治病，在广东慢性疼痛 MDT 专家交流平台准备就绪后，王家双教授结合自己 30 多年的临床经验，经过认真思考和征求意见后，建议 MDT 交流平台主要提供慢性疼痛多学科学术交流以及临床难治性疼痛病例为主。未来可以为区域各级医院疼痛诊疗技术提供指导、支持。拟定了先以疱疹后神经痛、三叉神经痛、椎间盘手术后神经痛和化疗后神经痛等疑难、顽固性疼痛专题和典型病例讨论，得到专家组的支持，也即刻吸引了多学科专家的目光和兴趣。

考虑到大家临床工作非常繁忙，专家组建议每季度开展一次活动，王家双教授提出初期由自己承担专题拟定，场地和支出，专题拟定后由 MDT 秘书征求大家意见后确定，后期再根据活动情况改变计划。同时平台向深圳、佛山、中山、东莞等地专家发出邀请信息。

发起人提议由中山一院疼痛科张劲军博士担任联络秘书，设立专线电话。后期又增加中山三院康复科陈曦博士和南方医大珠江医院康复科路鹏程博士为联络秘书。

初期每个季度举行一次，后期 2-3 个月一次。每次侧重一个专科与慢性疼痛，特别是顽固性神经痛诊疗，大部分情况下，许多专科求助疼痛科帮助分析、处理自己临床遇到的疑难疼痛病人。不仅体现了疼痛科医师的价值感，也促进了大家参与的积极性和主动性。5 年来，各专科提出了许多难治性疼痛需要疼痛科帮助，包括：疱疹后神经痛、中风后疼痛和枕神经痛（神经科）、椎间盘手术后神经痛（骨科）、化疗后神经损伤和晚期癌痛（肿瘤科）、骨质疏松症和颈、腰椎慢性疼痛（老年科）和脊髓损伤后疼痛、幻肢痛、交感神经疼痛（康复科）、三叉神经眼支疱疹后神经痛（眼科）以及许多难治性疼痛病例在 MDT 交流平台提出讨论，而疼痛科介绍的诊疗技术专题受到临床各科医师的欢迎和称赞。

2016 年底，由于各大医院参与专家的积极性高涨，纷纷要求参与承办，学术活动开始在广州各大医院轮流举行，再加上三位多学科秘书的努力工作，进一步使 MDT 活动进入

良性循环。至 2019 年底，通过全体 MDT 专家组支持、参与和三位博士秘书们的共同努力下，在丝毫没有耽误专家们自身工作的情况下，广东慢性疼痛 MDT 交流平台顺利完成超过 20 多期有针对性的专题疼痛学术活动。一位康复科博士代表参与者说出最使组织团队感动的话：只要有时间我一定要坚持参加每一期活动，因为每次参加不仅有新知识和见解，还解决了我们许多有关疼痛病的疑问。

四 慢性疼痛 MDT 交流平台的规模和范围

起初由于工作室活动空间的限制，MDT 交流平台限制 15 人左右，随着感兴趣的科室和医师逐渐增加，开始把交流场地转移到工作室外围，后期到各大医院举行，人数逐渐扩大范围。从开始只是科主任参加到普通医师和研究生或进修医师一起参与。目前 MDT 活动覆盖广州地区 80%的三甲医院和佛山、东莞地区 20 多家医院共计 11 个学科的临床专家共同参与。平台希望以后随着交通逐渐改善，周围远一些的城市也能够参与。

由于交流平台绝大部分专题涉及慢性疼痛诊疗内容具有趣味性和领先性，逐步引起广州地区各大医院的专科主任的高度兴趣，平台建立后的第二年，广州地区各医科大学附属医院、省和市级人民医院、中医院等单位共同支持，轮流举办不同主题，疼痛相关产品的公司、厂家也积极参与，共同给平台增添了无限的活力。

5 年间，MDT 学术活动仅限于广州地区的三甲医院，部分二级医院也希望能够举办。近年来，由于 MDT 逐渐扩大的影响力，部分外省、市医院也提出希望参与 MDT 交流活动。而发起人和组织团队希望未来广东慢性疼痛 MDT 交流平台的模式能够在国内其他地区或省、市大医院复制，这样不仅有利于疼痛科的发展，也能够促进兄弟学科疼痛诊疗技术的提高，能够帮助更多难治性慢性疼痛，特别是顽固性神经痛病人，为进一步和谐医-患关系做出贡献。

五、 MDT 的收获

广东慢性疼痛 MDT 交流平台建立 5 年多以来，除了疼痛科外，累计先后参与交流的科室还包括：神经科、骨科、康复科、中医科、老年科、肿瘤科、眼科、麻醉科、眼科和普外科等 10 个专科的医师。多学科专家从不同的角度探讨慢性疼痛的表现、影响范围和治疗方法，大大增加了大家对于慢性疼痛病的认识和理解，也开拓了疼痛科医师的视野，增加了多学科对于疼痛科的理解和支持。

1. 通过 MDT 交流平台和多学科专家团队的扩散，进一步扩大了疼痛科的宣传阵地和知晓度；

2. 神经科、康复科和骨科等学科邀请疼痛科参加专科年会和专题讨论会的专题讲课，交流和介绍疼痛科微创或介入治疗技术；

3. 各兄弟科室在本单位更多邀请疼痛科会诊和难治性疼痛病的交流、讨论，帮助疼痛科更好地相互融入和理解，促进了科室间的和谐、相互协作，化解了学科建立或发展阻力；

4. 通过相互学习多学科知识，促进了疼痛科规范化诊疗和医疗质量的改进，提高疼痛科的认可度和地位。

小结

5 年来，广东慢性疼痛 MDT 交流平台已经展现了多学科参与抗痛的生命力和对于促进区域疼痛科发展的优势。近年来，上海、贵阳、昆明、重庆等地区的疼痛科同道也分别对疼痛科主导的 MDT 表现出高度兴趣。进入 2020 年，由于抗击新型冠状病毒疫情的特殊情况需要，广东慢性疼痛 MDT 平台严格按照广州市政府的规定，推迟已经安排好的计划，除了微信外，暂时停止一切形式的面对面交流。为了 MDT 未来可持续开展，2021 年 4 月王家双教授和中山大学一附院冯霞等专家在广州发起成立了疼痛多学科管理专业委员会。在此希望各省、市专家能以参与抗击新冠疫情的各医疗专家团为榜样，不怕艰苦，坚持奉献，促进临床多学科交流，为攻克疑难疼痛病，创造无痛生活的目标共同努力奋斗！

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Cannabis Withdrawal

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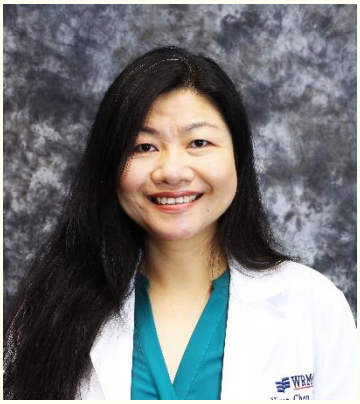
Introduction



Cannabis is the most commonly used illicit substance worldwide. Although commonly considered a "soft drug", cannabis use is associated with mental and physical health problems. As use of cannabis increases over the past 2 decades, more research efforts have advanced our understanding of not only cannabis use disorder, but also cannabis withdrawal.[1] Abrupt cessation of prolonged cannabis use can lead to a withdrawal syndrome, a new diagnosis included in the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) [2] and as a criterion for cannabis use disorder. Symptoms of CWS occur reliably following a specific time course with cessation of cannabis use, are transient, can be ameliorated by re-administration of cannabis, and are clinically significant.

Symptoms and Prevalence

Cannabis withdrawal syndrome (CWS) is diagnosed when within a week after cessation of heavy, prolonged use, ≥3 of 7 symptoms occur, including six behavioral or emotional symptoms and one or more of a list of physical symptoms (Table 1). It should be noted that if the symptoms are attributable to another medical condition or better explained by another mental disorder, including intoxication with or withdrawal from another substance, diagnosis of CWS is excluded. This makes the diagnosis of CWS even more challenging since the coexistence of mental disorder and other substance use disorder among cannabis users is not uncommon.[3-5] Onset of symptoms typically occurred between days 1-3, peak effects between days 2-6, and most effects lasted 4-14 days, similar to tobacco and other withdrawal syndromes.[6]

Table 1. Cannabis withdrawal symptoms

Irritability or aggression
Insomnia or unpleasant dreams
Depressed mood
Decreased appetite or weight loss
restlessness
Physical symptoms
Abdominal pain
Shakiness or tremors
Sweating
Fever
Chills
Headache

CWS was not included in DSM-IV-TR because its clinical significance was not recognized then. Budney *et al* proposed the existence of CWS and reported that more than 50% of adults seeking treatment for marijuana dependence experienced withdrawal symptoms.[7] Allsop *et al* demonstrated that CWS could be functionally impairing and patients with greater functional impairment were more likely to relapse.[8, 9] Another challenge to identify CWS is the lack of consensus on the best screening tool. Commonly used assessment instruments include the 22-item Marijuana Withdrawal Symptom checklist,[7] the Cannabis Withdrawal Scale,[8] the Marijuana Quitting Questionaire,[10,11] the Customary Drinking and Drug Use Record,[12] and clinical interviews involving the Time-Line-Flow-Back.[13] A recent meta-analysis which included 23,158 participants in 47 studies showed no difference in prevalence estimation using different ascertainment methods.[14] However, this does not mean that all instruments to assess CWS are equal. The inclusion of a diagnosis criteria in DSM-V will help to properly diagnose and treat CWS and prevent relapse.

The aforementioned meta-analysis [14] by Bahji and colleagues identified a pooled prevalence of CWS of 47% with significant heterogeneity among studies when the data source was stratified. Population based studies had the lowest prevalence of CWS of 17%, whereas outpatient and inpatient samples showed prevalence of 54% and 87%, respectively. Concurrent use of tobacco and other illicit drug was associated with significantly higher prevalence of CWS, as well as daily cannabis use. Like various individual studies, this meta-analysis did not reveal association between CWS prevalence and gender, age, race/ethnicity, or geographic region. Unlike multiple individual studies, this meta-analysis did not identify any association between CWS and psychiatric comorbidity. The authors, however, pointed out that cannabis use disorder (CUD) was more common among individuals with psychiatric comorbidity [15] including anxiety,[16] mood,[17] eating,[18] and psychotic disorders.[19, 20] The association between CUD and psychiatry comorbidity is generally negative, especially in the settings of younger cannabis exposure age and heavier cannabis use.[15] The overlapping symptoms between CWS and psychiatric disorder make the differential diagnosis further challenging. For example, patients with anxiety may use cannabis for the acute anxiolytic effect, and the anxiety experienced during abstinence maybe the manifestation of CWS, worsening of pre-existing anxiety, or the combination of both. Therefore, clinicians need to familiarize themselves with such association to provide patients with proper care and counseling.

Mechanism

Pharmacological studies identified delta-9-tetrahydrocannabinol (THC) as the primary psychoactive compound in cannabis that causes rewarding and addictive effect.[21] THC is a partial agonist of the cannabinoid receptor type 1 (CB1R).[22] CB1 knockout mouse model and pharmacological blockade of CB1R demonstrated its role in modulating cannabis dependence and withdrawal.[23, 24] Regular use of cannabis has been shown to desensitize and downregulate CB1R. This effect starts to reverse within 2 days of cannabis cessation and CB1R returns to baseline function within 4 weeks of abstinence, [25 - 26] which is consistent with the time course of CWS. Evidence supporting that THC plays critical role in CWS includes: 1) a hysteresis effect between the decrease in plasma THC and onset of CWS, [27] 2) withdrawal symptoms following oral THC, [28 - 29] and 3) alleviation of CWS by oral THC.[30] THC likely exerts its effect via a non-CB1R dependent mechanism as well. For example, animal study showed that THC increased the potassium-evoked dopamine release in the rat caudate neucleus.[31] More researches further

demonstrated that cannabinoids and endocannabinoids could modulate both voltage-gated ion channels (calcium, sodium, and potassium) and ligand-gated ion channels (serotonin type 3, nicotinic acetylcholine, and glycine receptors),[32] as well as cell membrane proteins and neurotransmitter receptors.[33] The exact mechanism of such modulation is not clear and more studies are warranted to provide potential treatment targets.

Although heavier cannabis users are more likely to develop CWS, some individuals develop CWS with short term, less than daily exposure. This raised the question whether genetic background predisposes certain individuals to withdrawal. Earlier genetic epidemiology studies focused on CUD and concluded that it was highly heritable.[34] For example, the San Francisco family study found that not only cannabis use, abuse, and dependence, but also age of first use were all heritable.[35] The same study also found that certain symptoms of CWS especially nervousness was heritable, too. More studies have been conducted since the inclusion of CWS in DSM-5. Twin study in Australia by Verweij and colleagues found that approximately 50% of variances in withdrawal were attributable to additive genetic factors (68% in abuse/dependence). The remaining variances were mainly due to unshared environmental influences.[36] The authors concluded that CWS is moderately heritable. More importantly, the genetic influences on cannabis withdrawal almost completely (99%) overlapped with those on abuse/dependence. This is reassuring for genetic informed studies that did not assess withdrawal.

Treatment

Cannabis withdrawal is considered a negative reinforcement for relapse and patients have reported using other substances such as nicotine and alcohol as a reliever.[6, 7, 10, 37] Therefore, much effort has been made to identify treatment options for CWS.

Despite the growing interests and positive results from small-scale trials, there is no approved pharmacological treatment for CWS, or CUD. Current candidates for CWS are either through the cannabinoid receptor, or other neurotransmitters.[38] The most studied cannabinoids are THC and cannabidiol (CBD). While THC has psychoactive activity thus a narrow therapeutic window, CBD lacks psychotropic property and is considered a promising candidate for CUD and CWS treatment.[21] Animal study showed that CBD alleviated withdrawal symptoms and reversed gene expression changes induced by cannabis withdrawal including opioid μ receptor (Oprm1), cannabinoid CB1 receptor (Cnr1) and CB2 receptor (Cnr2) in the nucleus accumbens in mice.[39] Further study is necessary to determine whether CBD has similar therapeutic effect in human subjects. THC was able to decrease the intensity of withdrawal symptoms in several studies, however, did not show efficacy in terms of abstinence maintenance in a recent metanalysis.[40]

Among non-cannabinoid agents, bupropion caught early attention due to its approval for tobacco cessation. Although cannabis and nicotine withdrawal share notable overlapping symptoms, bupropion was reported to worsen CWS symptoms.[41] Serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) produced mixed results based on both literature review and metanalysis.[39, 40] Some studies reported CWS symptom alleviation with SSRIs and SNRIs, while others showed no differenced as compared to placebos. Treatment with neither class resulted in increased likelihood of abstinence. Anticonvulsants such as gabapentin and topiramate showed promising results with decreased cannabis use and symptom intensity. However, studies so far are limited due to low power and poor completion rate.[39] Larger scale, fully powered studies are necessary to provide more conclusive evidence for the

role of anticonvulsants in treating CUD. N-acetylcysteine (NAC) is another agent of interest given its role in regulating glutamate release and preliminary favorable results treating cocaine and cigarette craving. NAC yielded positive primary cessation outcome in cannabis-dependent, adolescents and young adults (age 18-21) in both open-labeled pilot study [42] and double-blind, randomized control trial.[43] The same group replicated the study in adults (age 18-50) but could not reproduce the positive result, suggesting a possible age effect in treatment.[44]

While the search for pharmacological agents for CWS treatment remains ongoing, psychotherapy studies have established several evidence-based models and promising techniques in CWS/CUD treatment. Cognitive behavioral therapy (CBT), motivational enhancement therapy (MET) and contingency management (CM) are studied the most and have all shown benefits in cannabis use outcome (decreased frequency and quantity of use during treatment). And the combination of the 3 modalities has the highest efficacy.[45 - 46] However, abstinence rate remained modest and declined after treatment. Moreover, the increasing number of cannabis users, both recreational and medicinal, ensures that the volume of people developing CUD and/or experiencing CWS exceeds the capacity of substance abuse specialty services. Further investigation on brief intervention, computer/telephone-based intervention and social media may improve the accessibility of psychotherapy. Psychotherapy should also be incorporated with pharmacological therapy to improve the efficacy of CWS treatment.

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颊针治疗跟痛症一例

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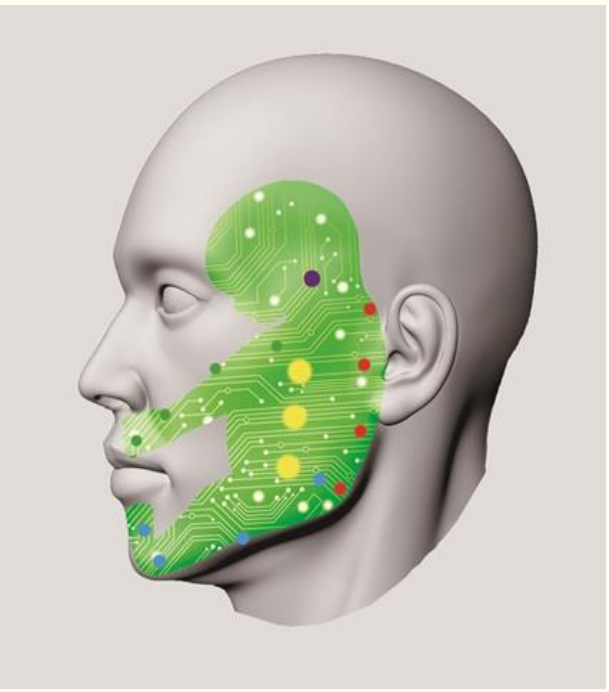
患者，女，49 岁，两周前双足跟部针刺样疼痛，行走多和站立多时加重，近两天疼痛加重，无法正常行走。在足踝门诊拍片无明显病变，诊断为双足跟痛症。查体：双侧枕下肌群压痛+++，双侧斜方肌压痛+++，下颈部压痛++，右膝关节后方压痛++，双足跟压痛+++。颊针取穴：头穴（双侧）、上颈穴（双侧）、颈穴（双侧）、背穴（双侧）、膝穴（右侧）、踝穴（双侧）和足穴（双侧）。留针 30 分钟，去针后上述部位压痛明显减轻，双足跟疼痛明显缓解，可以正常行走。颊针治疗后 10 天再治疗一次，临床痊愈。

跟痛症是指足跟周围疼痛为主要特点的一群症候的总称。该病发病率较高，约占疾病人群的 10%，约占足部疾病的 15% ，而且随着人口老龄化，跟痛症的发病率逐年上升。目前关于跟痛症的治疗方法很多，保守治疗主要方式有肢体牵张锻炼、理疗、足部矫形或肢体固定、药物治疗、注射药物封闭治疗、中医针灸推拿、针刀治疗等很多治疗方法，还有一些富含血小板血浆等新兴的方法。也有人认为当保守治疗半年以上而无明显效果时，应该考虑选择手术。但各种治疗效果不佳，止痛效果差，病程长，容易复发。[1]

颊针疗法是王永洲教授及其团队经过二十八年的临床实践及研究创立总结的全新微针理论技术体系，通过针刺面颊部特定穴位治疗全身疾病的一种无痛针灸新疗法。颊针疗法具有“取穴标准、靶点明确、治疗广泛、操作简单、无痛安全”的特点，使之成为与时俱进符合时代节奏的新方法，同时也为针灸学的发展提供了一种新的培养模式，大大提高了针灸疗效的可重复性，任何水平的中、西医师经过规范化的培训都能够很好地掌握。颊针疗法通过以解剖为基础对应的全息层面，以四肢和脊柱的颈肩腰腿痛疼痛为主要对象，多为常见病、多发病，是颊针的有效治疗病种。颊针疗法治疗跟痛症具有快速起效、作用长久、复发率低的特点，在目前治疗的患者中取得了很好的疗效。颊针疗法为治疗跟痛症提供了一种全新的治疗方法。[2]



颊针定位穴位简单准确　颊针的穴位定位根据人面部骨性特征定位，比如颧弓根上缘就是颈穴的位置，拍针颈穴可以治疗落枕和颈部肌肉疼痛等疾病。颊针疗法为广大跟痛症患者提供一种有效、安全、方便和快捷的治疗方法，体现了中医的博大精深。[3]

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POCUS 讲座

ASA Diagnostic POCUS Certification Program

Wang Hong, MD

In 2018, ASA formed an Ad Hoc committee regarding diagnostic point-of-care ultrasound (POCUS) to explore a way to support the rights of POCUS practice by anesthesiologists and provide the guidance of the scope of practice and minimum POCUS training requirements.

The Ad Hoc committee affirmed the AMA 1999 position of "ultrasound imaging is within the scope of practice of trained physicians" and "hospitals should grant privileges to perform ultrasound (US) imaging in accordance with specialty-specific guidelines". The committee proposed primary and secondary scopes of perioperative diagnostic POCUS. The primary scope includes focused cardiac ultrasound, focused gastric ultrasound, and focused pleural/pulmonary ultrasound. The secondary scope includes focused airway ultrasound, focused assessment with sonography in trauma (FAST exam), focused musculoskeletal/soft tissue ultrasound, focused ocular ultrasound, focused renal/GU ultrasound, focused transcranial Doppler ultrasound, focused ultrasound for deep venous thrombosis. The primary scope is part of the ACGME training requirements and ABA exam contents. The secondary scope is relevant to certain subspecialities and / or in special situations.

The committee also made the recommendations for the minimum requirement of supervised studies.

		Personally Performed	Personally Interpreted
Primary Scope	Cardiac	50	100
	Gastric	30	20
	Pleural/Pulmonary	30	20
Secondary Scope	Airway	30	20
	FAST	30	20
	Musculoskeletal/Soft Tissue	***	***
	Ocular	***	***
	Renal/GU	30	20
	Transcranial	100	n/a
	Deep Venous	30	20

***Indicates areas where there is insufficient data for recommendation.

The Current ASA Diagnostic POCUS Certification Program is focused on the primary scope: Focused cardiac, gastric, and pleural/pulmonary ultrasound. Starting from January 1st, 2022, FAST will be included in the primary Scope and the POCUS Certification Program.

The certification includes five components.

Part 1: Develop a "game plan" to achieve the individual goal for improvement of the practice. This part also includes seven questions. The purpose of this is to qualify the MOCA part 4 requirement.

Part 2: Diagnostic POCUS training. This can be accomplished through training during residency or fellowship or participating in an ASA- approved program. The approved programs include ASA POCUS certification workshop during the annual ASA meeting. The ASA POCUS certification website also includes many other programs such as POCUS or Echo workshop offered by ASRA, SCCM, SCA.

Part 3: Image Interpretation Training. This is an Online Case-Based Diagnostic POCUS Module. The module starts with literature review and then Q and A case-based questions. Currently, the interpretation is focused on the 2D images.

Part 4: Image Acquisition Training. The purpose of this is to demonstrate your ability "to obtain standardized, interpretable clips". It requires 30 lung ultrasounds, 30 gastric ultrasounds, 50 focused cardiac ultrasounds images. It is not necessary to submit the pathologic images. You can either submit to an approved "local" mentor or ASA faculty. There is a fee difference between the local mentor and ASA faculty mentor.

	Member Price		Non-Member Price		Resident/Fellow Price	
	Local Mentor	ASA Faculty Mentor	Local Mentor	ASA Faculty Mentor	Local Mentor	ASA Faculty Mentor
Price	$1,000	$1,400	$1,600	$2,200	$400	$560

*Local mentor qualification: Meet one of the following and approved by ASA POCUS Certification Editorial Board.

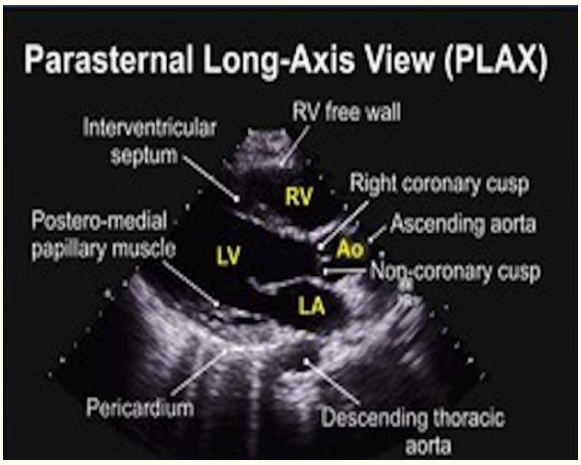
- A national certificate in relevant POCUS organ system(s) cardiac, lung, gastric ultrasound
- Served as a faculty at a POCUS CME course
- Personally performed and interpreted a specific minimum number of POCUS exams in the relevant organ system (150 cardiac, 50 lung, 50 gastric)
- Director of POCUS in your department/division/practice area

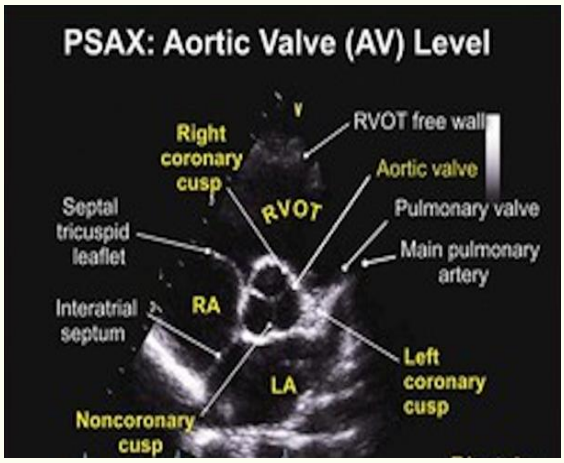
I am an approved local mentor and will be happy to help anyone who wishes to obtain the certification.

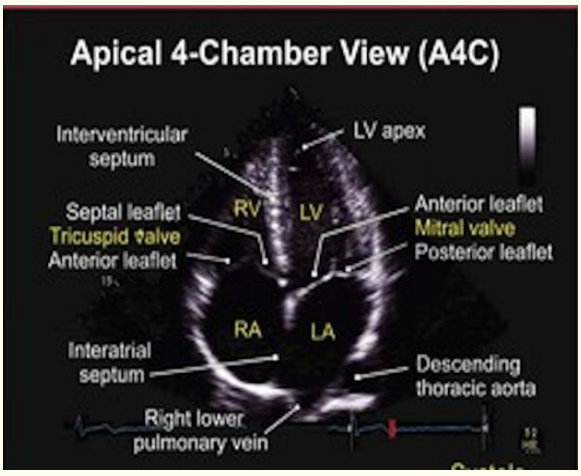
Part 5: Take the 2-hour exam. The exam contents include POCUS fundamentals, as well as cardiac, gastric, and lung image interpretation. Each section of the exam can be taken independently at different times. The required passing score is 70%.

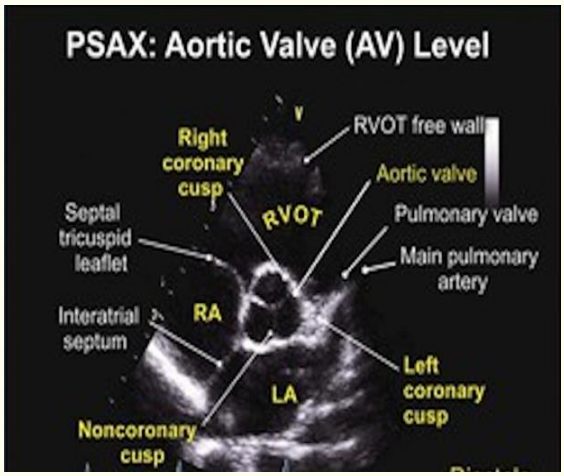
Examples of Diagnostic POCUS Ultrasound:

1. Focused Cardiac US:

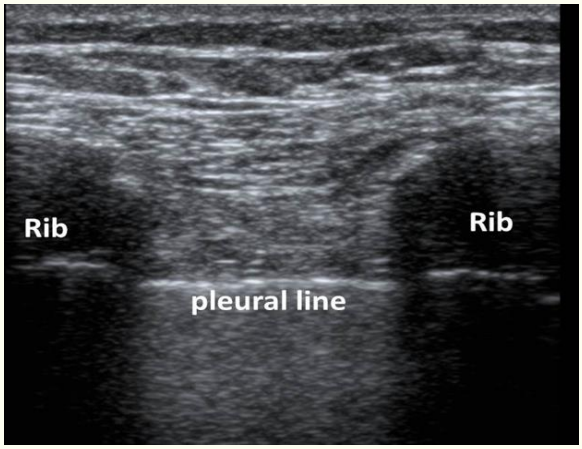


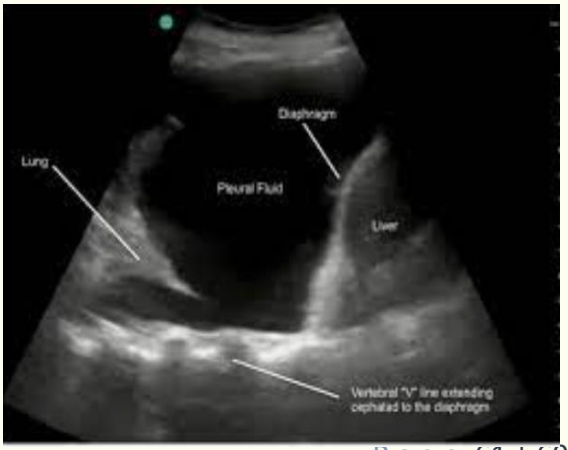




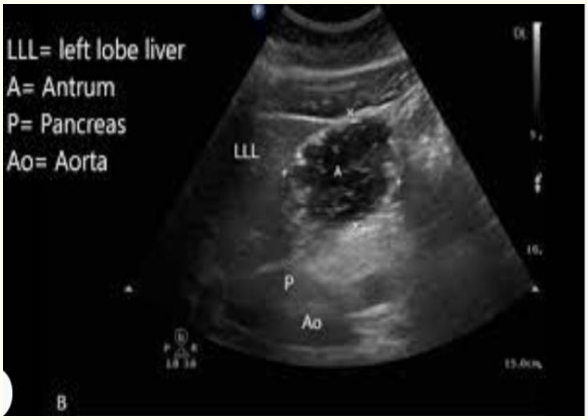


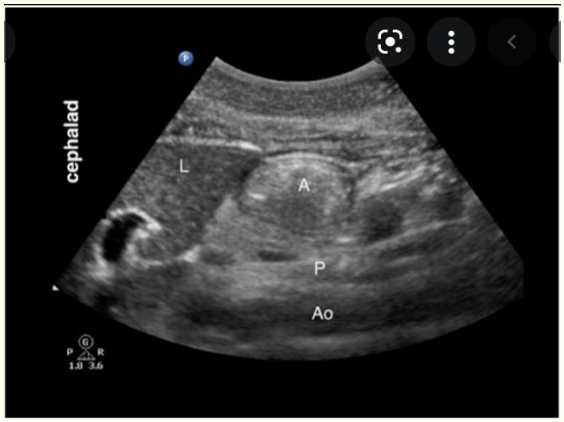
2. Focused Pleural/Pulmonary US:



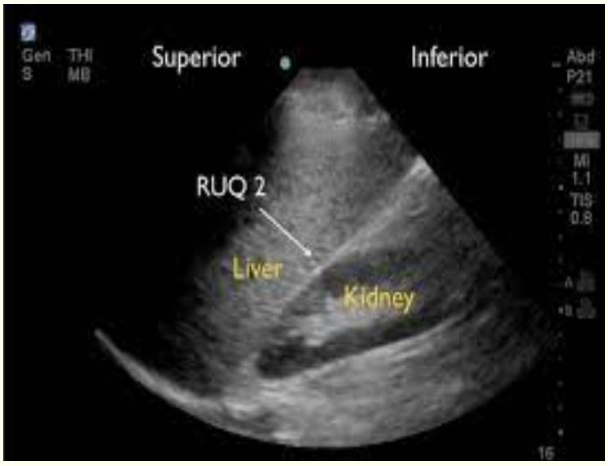


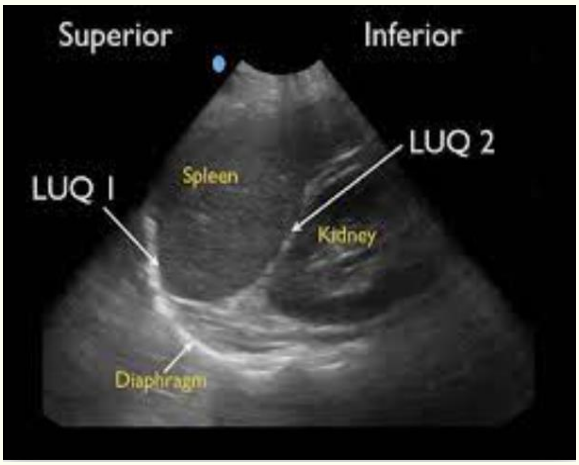
3. Focused Gastric US: Full Stomach

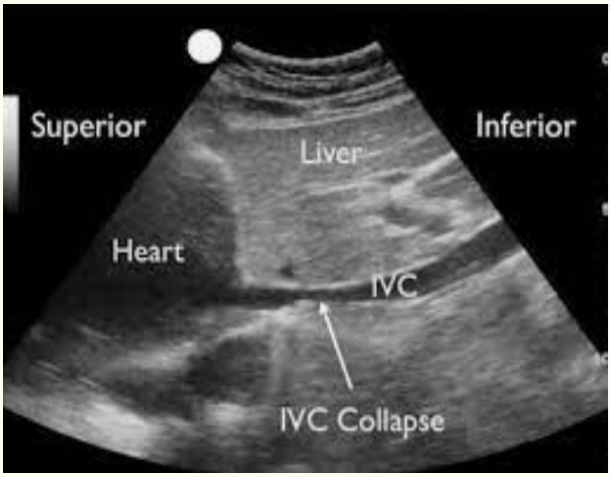


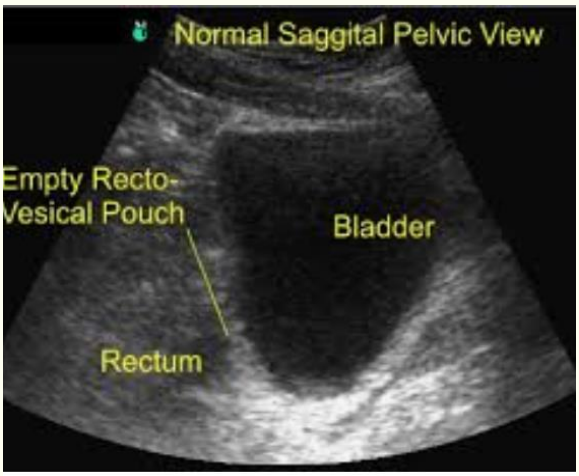


4. FAST









CASA ZOOM 会议-2

聊聊麻醉：困惑和策略-2

苗宁 MD

CASA 的线上讨论会之二在黄建宏主席的倡议下于 10/2/2021 19:30 在 Zoom 上又一次成功举办并圆满完成。这一次大家聊的主要话题是“工作减缓”。

晓燕主持会议。她指出我们 CASA 许多麻醉医生大都行医超过 20 年，并且 2/3 的医生年龄也超过 50 岁。许多人正在考虑走入人生的下一个阶段：即分阶段逐渐减缓工作步伐或考虑退休。而如何从心理或生理上顺利、平稳地过渡是这一期会议的主题。

许多医生认为之所以慢慢减缓工作步伐，主要有以下几个原因。一.身体因素：长期超负荷运转身心疲惫， 尤其是夜班，周末和节假日值班尤甚；二.家里的负担减轻，经济实力稳定，工作时间降至 60%收入对生活无甚影响； 三.COVID 肆虐不得不减少工作量；四.追求一直想做而不能做或无时间做的业余爱好，典型的例子是陶青医生退休后享受帆船运动，阅读，画画和弹琴，生活其乐滔滔，困惑她已久的病痛也在不知不觉中消失无踪；五.提高生活质量和增加休恬时。慢走，唱歌，跳舞，摄影，修图，打球，园艺，钓鱼，投资等等让大家终于享受生活的美好和身心的健康。

如何与麻醉科或医院商讨减缓步伐的可能性？这由各个工作单位拟定：有些单位工作 50%以上就可享受全部保险;有些单位允许多个医生轮流工作超过 60%算全职并享受各种保险；有些医生采取较自由的 Per Diem(计日工作)方式而自己购买保险。有些人转换跑道，从必须值班的医院换至值班少的医院或不需值班的“日班外科手术中心”工作；有些人由于手术医生的需要而“友情”工作；有些人由于不太愿意与医院商讨这些细节，经济状况也十分稳定，干脆提出退休。

如果减缓工作，健康保险如何保证？答案是大学医院工作的同行由医院为员工购买保险；而大多数私立医院工作的麻醉医生已习惯于自我购买各种保险，65 岁以后两者都由 Medicare 保险接管。吴多平医生认为不管从事哪种麻醉工作，一定要确保经济状况的稳定性和预先计划退休金的购买。他认为税表 W2 和 1099 对于退休金的优惠方面有极大的区别，1099 税表允许大家将一半或以上的工资购买退休金，这样既可快速增长退休金额，又可减少税率，还可增加投资。后续麻醉界的投资专业人员将会有更专业化的讲解。

会中大家一致同意，我们这一代是拼搏、幸苦而又实现自我的一代，大家生活稳定，经济优越，享受“夕阳红”是我们每人即将到来的主要任务，所以要尽量保持身心康健，精力充沛和体力旺盛。

今天的会议让已工作减缓的医生们充分展示了他们的“优惠结果”，也让尚未减缓的医生有了“指路明灯”和朝之努力的方向。

麻醉医生的金融小知识

楼燕勤， 美国加州麻醉医师

前段时间 CASA 举行了一场别具一格的有关退休及其理财方面的论坛活动。当时我刚好在葡萄牙自驾游玩而遗憾错过。

有些成员已知我基本退休已一年多了，希望了解一些我的情况和想法以作借鉴或参考。基于上述，我非常荣幸能有机会分享我的感想与体会。许多也是个人的经验教训，现总结如下。希望对大家有点启示性帮助。若有不当之处，敬请大家指正。我们可以互相讨论，共同提高。

1. 需要并必要学习一些金融基础知识和概念

我们在美国做医生，熟悉医学专业知识。但总体来说，对美国的个体或公司的账务、税务、保护、投资、金融及其管理方面等知识比较缺乏。为此，花些时间学习一些基本知识，尤其是基本概念十分必要，如 Basic finance，How money works 等等。了解了一些基本概念与知识后，再找专业人士咨询就相对容易理解和沟通，这样才有可能与之有效地进行探讨，以找到最合适于自己或自家的方式、方法、规划和计划。

2. 专业问题要找专业人士与专业团队咨询和帮助

医生们的学习能力均十分高强。但几无可能成为各方各面的专家。就象病人未曾上过医学院，可以自学很多书本医学理论知识，但仍然不能为自己诊治疾病。找到专业上有实践经验加之良好的伦理与职业道德的专业人士，专业合作的团队对家庭和各人的总体策略，各个阶段规划，具体计划的选择与追踪调整具有极其重要作用。

3. 需尽早尽快行动

越早越年轻，可做的选择越多并且自动性和灵活性越大。更重要的是能充分使用和体现时间的价值。如果快到退休年龄再考虑计划时，选择余地较有限，即使有花费也昂贵到近乎离谱。因此在年轻时把握以下的优先考虑非常关键：什么事是最重要、紧迫、紧急、必需等，以及它们之间的配对关系之选择。

我们大多数在此群的还是属于第一代的美国华人。很多以前太忙未能做好这些的，现已到或接近退休年龄了，是否就已彻底无戏可唱了？我相信天无绝路。应该有例外，比如资本累积已达超高水平，或者为家中儿女考虑，或资产传承，税务考量等等，这些若能得到资深经验专业人士的特殊处理也许会带来意想不到的结果。探索不会有害无益！

4. 需与专业人士时刻保持有效沟通，坦诚交流，充分探讨和合作

有时作为医生的我们常以为他们告诉我们的信息已理解清楚了，或者认为自己独立做即可。但其实真的是没懂或没能深刻领会，特别是年轻身强力壮时，加上工作学习繁忙时期，很难有耐心与精力去体会。有时需经过相当一段岁月的磨炼才能真正领会。因此找到合适的专业人士后，我们需要给予信任。就象我们在手术前给病人讲各种麻醉方法和选择以及利弊等，绝大多数人是把信任给予我们，相信并让我们为他们的最大利益做个体化选

择麻醉方案和计划，我们给他们讲清楚利弊，以及对可能出现的弊的预防及应对措施，包括病人与家属和医护人员各自可以做、尽力需做的或合作协助做的道理是一样的。这样使患者和家属都能理解和参与，以达到最佳结果。在医学上如此，在理财方面其实也类似。不可能找到或复制一个是最好的又合众口的计划，而只有找最适合某个体情况与特点的又最符合此个体的需求计划！个案需要个体化设计，非常重要，而这需建筑在相互的信任、充分的了解与理解基础上，全面并动态地分析，最终选择其个体或家庭在某一特定阶段的长期、中期与短期需要和目标的策略和规划。

5. 社会大环境的影响

个人或家庭的各种经济或财务情况，离不开美国的社会、经济和法律及其发展趋势和现状，更离不开个人及商业的税务与财务的众多复杂的政策和规定，并且涉及有关退休年令及退休后一些政策和措施的变化。因此当我们作这方面准备时，根据需要，有时必须有多方面的专业人士及团队帮助，比如会计师、精算师、金融人士、财务规划师、律师等等，如同医学上有家庭医生和其他各专科医生一样。找到合适的、可以较容易沟通进行舒适工作的专业敬业人士及其团队运作，将是最不容易但最值得花时间探索寻找的。注意：首先宏观与全面考量，然后再精选细挑。并且注意动态地查看与调整。

作为咱们华人，考虑到文化和传统上的一些差异，需排除迷信或讳忌话题的心理负担也是十分重要的。有备无患，有备则安。

6. 退休只是人生另一阶段的开始

人生得失永远存在，重在于选择和适应，生活与情趣，责任与义务。没有一成不变的规矩。想做的，有能力做的，开心做的，有益于家庭孩子配偶亲人的，又有益于人类健康和平幸福友谊的，多多益善，不拘形式！安排好自己的财务与未来，不给最爱自己或自己爱的人和家庭增加负担，减少对社会的依赖，从某种意义上说，也是对社会的一种贡献。若在此基础上能给予和无自我经济压力去探索，协助创造新的人生篇章，那将更是值得憬幢的美景！

以上是我个人的一些肤浅感想与体会，供大家评阅参见并敬请指教！限于文笔水平，请多包涵。

2021 年 11 月 17 日于加州尔湾。

CASA ZOOM 会议-3

术中低血压以及对器官潜在的影响

苗宁， 彭勇刚，MD

CASA 的线上“聊聊麻醉：困惑与策略”讨论会之三在黄建宏主席的倡议下于 2021 年 11 月 13 日 19:30 通过 Zoom 网络平台在线上再次举行。这是本年度 CASA 最后一次线上学术讨论会。这次大家聊的主要话题是“术中低血压的麻醉管理以及对重要脏器的潜在的负面影响”。

汪红和孟令忠教授共同主持此次的研讨会，并诚挚邀请了多位在美临床实践的麻醉专家学者与大家一起讨论和分享他们各自工作中的经验和体会。他们包括有彭勇刚，左志义，刘恒意，李成付和仲巍等教授。除了这些教授的发言，将近 40 名医生参与和聆听了此次讨论。有些参与者也都各抒己见，畅所欲言，踊跃参与讨论,提问和讲述各自对于术中血压管控的体会和见解。虽是学术讨论，但是并未感觉拘谨，气氛十分活跃。再次充分体现了在美华人医生对知识的追求和协会组织的凝聚力。

首先大家最关心，也是最困惑的是：如何定义术中平均动脉压（MAP）？65、70、75、 80mmHg？什么是低血压的危害？虽然有大数据的结果分析；有高、低和正常血压范围的书本和文献定义和有各自工作时积累的经验，但至目前为止，大家仍然对低血压的确切数值未能达成完全共识。

孟令忠教授认为：人体生理状态时，白天血压 135/80 mmHg 左右，夜晚血压降低 15-20% 大都无任何不良影响。相反，不能保持这种生理状态下昼夜周期变化的患者，反而会出现早期器官的损伤。有时降低外周阻力可见动脉血压下降，但随之心输出量增加反而可以改善器官灌注。血压值下降到影响任何重要器官的灌注流量，导致器官功能受损就是低血压，但我们现在的“缺陷”是不能即时监测器官血流量的改变。他认为关注人体器官的自主调节阈值也十分重要，血压接近器官自主调节的下限时要警惕器官灌注量的降低，术中血压降低还要分析各种影响原因：心脏前负荷、心率、心律、心肌收缩力还是外周阻力的改变，并调整相应的治疗方法和治疗药物。血压的维持也与手术类型、创伤大小、病患的年龄、基础血压、身体已有疾病状况有关。他应用一例术中 MAP 没有维持在 65mmHg 以上的患者，在实施肩关节手术后发现大面积脑梗塞的病例来提醒大家，血压的高低维持应综合考虑，而非仅是血压绝对值的高低。

彭勇刚、高卫东、黄佳鹏等教授也同样认为：病患术中血压无统一“正常”指标。体循环血压的高低不等同于器官灌注压和器官灌流量的多少。器官灌注压和器官灌流量是两个相关而不相等的理念。器官灌流量与循环血量、外周血管阻力、心脏收缩力以及心、脑、肾自主压力的调节密切相关。我们对大脑压力自主调节认识相对清楚，但是对心脏肾脏等器官的自主压力调节认知贫乏。 低血压的严重度和时间长短对器官灌注量的改变以及对器官的损伤有重要影响。使用血管活性药物时要考虑身体在应激状态下自身释放的血管活性物，如果应用外源性血管活性药的药理性帮助升高和维持血压却忽视容量状态，一味追求体循环血压而大量使用活性药物，对身体也有毒副作用。由于目前尚无直接即时监

测器官血流量和代谢产物的仪器，所以围术期的血压维持也应综合分析患者病情，个体调控。与外科医生的术前讨论手术方法以及围术期的有效沟通也及其重要。

刘恒意教授指出，如何灵活正确维持术中血压至关重要。血压高增加出血可能性，血压低可致重要器官供血不足而使之功能受损，如何在二者之间找到平衡点？他并强调注意术中血压的变化与凝血状态和病患的基础血压以及原有的合并疾病严重性息息相关。

李成付教授根据其骨科麻醉的临床特点和经验，建立了其医学中心围术期骨科麻醉不同术式的相关流程，并与外科医生达成共识，取得较满意的效果。他们制定了肩关节手术时 MAP 维持在病患的基础血压在 20% 范围内，并在术前 IV 补液 1L；关节镜手术维持 MAP 在 65mmHg 左右；脊柱手术血压维持在基础血压的 10% 左右而未见血压改变所致的并发症。术中病患出血和低血压时，除了输血补充血容量外，还给予 5% Albumin，钙剂，Ephedrine 和 Phenylephrine 升高血压，当 Phenylephrine 用量超过 1mg/kg 后，改用 Norepinephrine IV 滴注维持血压。他指出脊柱术中出血与手术本身、病患体位、胸腹压力均相关。他也强调血压的调控要个体化分析和处理，但有麻醉流程后便于与外科医生讨论、分析和管理术中血压的改变。

仲巍教授讲述小儿麻醉时的血压管控与成人的几点不同：小儿平均血压的正常值和血容量随年龄不同而变；小儿术中出血量超过 20-30% 有时血压仍表现为代偿性“正常”，如果不及时处理，可能出现不可逆转的后果。 所以血压并非唯一监测指标，还应观测粘膜，皮肤充盈度和其他指标。

左志义教授在临床和科研上的成就有目共睹。他引用了一些其他院校的临床科研结果，一些前瞻性的研究以及他自己团队的科研结果证明，术中病患 MAP 如能维持在 50-90mmHg 范围内，术后病人的谵妄和认知功能障碍的发生率无任何明显不同；多中心的研究在腹腔手术全麻超过 2 小时，发现吸入麻醉剂降低血压程度大于静脉麻醉（TIVA），但尽管如此，术后认知功能障碍也无明显区别。左志义教授的科研团队发现 0.4 MAC 的 Sevoflurane 虽降低血压，但可直接扩张脑血管并使脑灌注量增加；1MAC 的吸入麻醉剂可抑制 50 - 60% 的大脑细胞代谢率（O_2需求量）。颅脑手术时如 SSEP 或运动功能受抑制，增加血压可改善之，血压、脑灌注量和灌注压同样重要。他也承认难以界定血压值多高为正常血压。

汪红教授谈及“低血压预测指数（HPI）”的进展。这种方法根据动脉压波形、02 饱和度可大致预测 15 分钟后血压变化的可能性。黄佳鹏教授认为此法重点仅监测血压值，很难据此推断出准确的围术期血容量和器官灌注压的相应变化，未来还应有大数据的研究结果和人工智能等其他监测手段的运用来印证低血压预测的可行性。

讨论会延续了两小时之久。最后汪红教授总结道：此次的讨论会纯学术性，讨论术中血压如何管控而不损害病患器官功能。大家一致认为血压非唯一监测脏器灌注量的指标，低血压所致的危险不容忽视，血压的维持应“个体化”管控。

黄建宏主席向大家谈及明年的 CASA 主席将会在 2022 年一月由曹锡清医生出任并带领大家继续前行，他希望大家支持新主席的工作，并希望类似的麻醉学术讨论会继续延续下去！

独自惜幽芳，不敢矜迟暮。　近. 王国维
摄影：Catherine W. 摄影群

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