MEDICAL SPECIALTY BOARD REVIEW

# Pain Medicine

## BOARD REVIEW

Edited by

Marc A. Huntoon

OXFORD

# PAIN MEDICINE BOARD REVIEW

# PAIN MEDICINE BOARD REVIEW


EDITED BY

*Marc A. Huntoon, MD*

PROFESSOR OF ANESTHESIOLOGY

VIRGINIA COMMONWEALTH UNIVERSITY

RICHMOND VIRGINIA



OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS

Oxford University Press is a department of the University of Oxford. It furthers the University's objective of excellence in research, scholarship, and education by publishing worldwide. Oxford is a registered trade mark of Oxford University Press in the UK and certain other countries.

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America.



Library of Congress Cataloging-in-Publication Data
Names: Huntoon, Marc A., editor.
Title: Pain medicine board review / edited by Marc A. Huntoon.
Other titles: Pain medicine (Huntoon)
Description: Oxford ; New York : Oxford University Press, [2017] |
Includes bibliographical references and index.
Identifiers: LCCN 2016029256 (print) | LCCN 2016029915 (ebook) |
ISBN 9780190217518 (alk. paper) | ISBN 9780190217525 (e-book) |
ISBN 9780190217532 (e-book) | ISBN 9780190217549 (online)
Subjects: | MESH: Pain | Pain Management | Examination Questions
Classification: LCC RB127 (print) | LCC RB127 (ebook) | NLM WL 18.2 |
DDC 616/.0472076—dc23
LC record available at https://lccn.loc.gov/2016029256



1 3 5 7 9 8 6 4 2
Printed by WebCom, Inc., Canada

# DISCLOSURES

The views expressed in Chapters 12 and 24 are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

# CONTENTS

# PREFACE

I undertook the writing of this book because of what I perceived as a gap in the available board review books at the time of my last recertification in pain medicine. There were a couple of books out then, but they seemed to be less focused on the actual key words and examination content outlines produced by the American Board of Anesthesiology (ABA) and other parent boards. As a former question writer for the ABA exam, I was well aware of the goals of those who develop those board exams. Despite the dearth of available review books, I (fortunately) did not find the exam to be too difficult. However, as someone who has led pain medicine programs at institutions such as the Mayo Clinic, Vanderbilt University, and now Virginia Commonwealth University, one should expect that academic faculty would stay abreast of the information relevant to a modern pain practice. The field of pain medicine has continued to evolve during the quarter century that I have been practicing, and the need for leadership in education has not lessened. Although no one book can be a sole source of study material for such an all-encompassing specialty area, it is my hope that this book will help medical students become interested in the field and that residents, fellows, or recertification candidates would become familiar enough with the material that they could pass the examination. I wish you the best, and hope that you find this field to be as fulfilling as I have, while remaining cognizant of the privilege it is to serve patients in pain. We must first be humble and strive to become knowledgeable to be the best we can.

Marc A. Huntoon, MD

# CONTRIBUTORS

**Ignacio Badiola, MD**
Assistant Professor of Anesthesiology and Critical Care
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA

**William A. Beckman, MD, CAPT, MC, USN**
Assistant Professor of Anesthesiology
Uniformed Services University of the Health Sciences
Staff Anesthesiologist and Pain Medicine Physician
Naval Medical Center Portsmouth, Virginia

**Markus A. Bendel, MD**
Department of Anesthesiology
Division of Pain Medicine
Mayo Clinic
Rochester, Minnesota

**Gregory Carpenter, MD, MBA**
Department of Anesthesiology
Vanderbilt University
Nashville, Tennessee

**John Corey, MD**
Assistant Professor of Clinical Anesthesiology
Division of Pain Medicine
Vanderbilt University
Nashville, Tennessee

**Bryan Covert, MD**
Pain Medicine Fellow
Department of Anesthesiology
Vanderbilt University
Nashville, Tennessee

**Kurt F. Dittrich, MD**
Assistant Professor of Clinical Anesthesiology
Division of Pain Medicine
Vanderbilt University
Nashville, Tennessee

**David A. Edwards, MD, PhD**
Assistant Professor of Anesthesiology
Vanderbilt University
Nashville, Tennessee

**Ian M. Fowler, MD**
Assistant Professor of Anesthesiology
Uniformed Services University of the Health Sciences
Staff Anesthesiologist and Pain Medicine Physician
Naval Medical Center San Diego
San Diego, California

**Amitabh Gulati, MD**
Director of Chronic Pain
Assistant Attending, Department of Anesthesiology
and Critical Care
Memorial Sloan Kettering Cancer Center
New York, New York

**Robert J. Hackworth, MD**
Division of Pain Medicine
Naval Medical Center
San Diego, California

**M. Gabriel Hillegass, III, MD**
Assistant Professor of Anesthesiology
Division of Pain Medicine
Department of Anesthesia and Perioperative Medicine
Medical University of South Carolina
Charleston, South Carolina

**Joshua Horowitz, DO**
Pain Medicine Fellow
Department of Anesthesiology
Vanderbilt University
Nashville, Tennessee

**Joseph C. Hung, M.D.**
Interventional Pain Management Physician
Tripler Army Medical Center
United States Department of Defense
New York, New York

**Elizabeth Huntoon, MS, MD**
Assistant Professor Physical Medicine and Rehabilitation
Assistant Professor Orthopedic Surgery and Rehabilitation
Director of Physical Medicine and Rehabilitation Medical Student Education
Vanderbilt Medical Group
Nashville, Tennessee

**Adam K. Jacob, MD**
Associate Professor of Anesthesiology
Mayo Clinic
Rochester, Minnesota

**Usman Latif, MD, MBA**
Assistant Professor of Anesthesiology
University of Kansas School of Medicine
Kansas City, Kansas

**Daniel F. Lonergan, MD**
Assistant Professor of Clinical Anesthesiology
Division of Pain Medicine
Vanderbilt University
Nashville, Tennessee

**Maureen F. McClenahan, MD, CDR, MC, USN**
Assistant Professor of Anesthesiology
Uniformed Services University of the Health Sciences
Director of Pain Medicine, Department of Anesthesiology and Pain Medicine
Naval Medical Center
Portsmouth, Virginia

**Kelly McQueen, MD, MPH**
Professor of Anesthesiology
Division of Ambulatory Anesthesiology
Director, Vanderbilt Anesthesia Global Health & Development
Vanderbilt University
Nashville, Tennessee

**Neel Mehta, MD**
Medical Director, Pain Medicine
Department of Anesthesiology
Weill Cornell Medical College
New York-Presbyterian Hospital
New York, NY

**Susan M. Moeschler, MD**
Department of Anesthesiology
Division of Pain Medicine
Mayo Clinic
Rochester, Minnesota

**Ramana K. Naidu, MD**
Assistant Professor of Anesthesia & Perioperative Care
University of California, San Francisco
San Francisco, California

**Andrea L. Nicol, MD, MS**
Assistant Professor of Anesthesiology
University of Kansas School of Medicine
Kansas City, Kansas

**Ryan Nobles, MD**
Assistant Professor of Anesthesiology
Division of Pain Medicine
Department of Anesthesia and Perioperative Medicine
Medical University of South Carolina
Charleston, South Carolina

**Daniel Pak, MD**
Resident
Department of Anesthesiology
Weill Cornell Medical College
New York-Presbyterian Hospital
New York, NY

**Meenal Patil, MD**
Pain Management Center
Trenton, New Jersey

**Julie R. Price, PsyD**
Co-Interim Director for Health Psychology Services
Osher Center for Integrative Medicine at Vanderbilt
Assistant Professor of Clinical Psychiatry
Assistant Professor of Physical Medicine & Rehabilitation
Vanderbilt University School of Medicine
Nashville, Tennessee

**Micah J. Price, PsyD**
Director, Department of Psychology
Broward Health Medical Center
Assistant Clinical Professor of Psychology
Coordinator of Internship Training and Liaison Services
Nova Southeastern University
Fort Lauderdale, Florida

**Antonio Quidgley-Nevares, MD**
Associate Professor and Chairman of Physical Medicine & Rehabilitation
Staff Physiatrist and Pain Medicine Physician
Eastern Virginia Medical School
Norfolk, Virginia

**Ellen W. K. Rosenquist, MD**
Assistant Professor of Anesthesiology
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Cleveland, Ohio

**Martha J. Smith, MD**
Assistant Professor of Anesthesiology
Division of Pain Medicine
Vanderbilt University
Nashville, Tennessee

**Christopher Sobey, MD**
Assistant Professor of Clinical Anesthesiology
Division of Pain Medicine
Vanderbilt University
Nashville, Tennessee

**Natalie Strickland, MD**
Assistant Professor of Anesthesiology
Emory University School of Medicine
Egleston Children's Hospital
Atlanta, Georgia

**Hans P. Sviggum, MD**
Medical Director, Obstetric Anesthesiology
Mayo Clinic
Rochester, Minnesota

**Drew M. Trainor, DO**
Denver Back Pain Specialists
Greenwood Village, CO

**Anthony A. Tucker, MD**
Assistant Professor of Anesthesiology
Uniformed Services University of the Health Sciences
Staff Anesthesiologist and Pain Medicine Physician
Naval Medical Center
Portsmouth, Virginia

**Erik P. Voogd, MD**
Division of Pain Medicine
Naval Medical Center
San Diego, California

**Jenna L. Walters, MD**
Assistant Professor of Clinical Anesthesiology
Division of Pain Medicine
Vanderbilt University
Nashville, Tennessee

**Aaron Jay Yang, MD**
Assistant Professor of Physical Medicine and Rehabilitation
Vanderbilt University
Nashville, Tennessee

**Robert Yang, MD**
Washington, DC

# 1.

# PAIN ANATOMY AND PHYSIOLOGY

*Daniel J. Pak and Neel Mehta*

## INTRODUCTION

This chapter focuses on pain anatomy and physiology to provide a comprehensive review of the mechanisms of nociception for preparation of the American Board of Anesthesiology Pain Medicine (PM) Examination. It reviews the anatomy of pain pathways (particularly the spinothalamic sensory tract) and the process of pain conduction from peripheral nociceptors to the cerebral cortex. It also reviews the different mechanisms of sensitization and inhibition at peripheral nociceptors (manifested as primary and secondary hyperalgesia), the spinal cord (wind-up and sensitization of second-order neurons), and supraspinal structures, which all affect the processing of nociceptive signals in the nervous system and, ultimately, the perception of pain.

## QUESTIONS

**1. Which of the following statements about nociceptors is false?**

A. Silent nociceptors respond to inflammation.
B. Polymodal nociceptors are the most prevalent type.
C. Mechanonociceptors respond to pinch and pinprick sensations.
D. After repeated stimulation, nociceptors may demonstrate sensitization.
E. Nociceptors have low thresholds for activation.

**2. Arrange Aβ, Aδ, and C nerve fibers from the fastest to slowest conduction velocities.**

A. Aβ, C, Aδ
B. Aβ, Aδ, C
C. C, Aβ, Aδ
D. C, Aδ, Aβ
E. Aδ, Aβ, C

**3. The following are true statements regarding abdominal visceral pain except:**

A. Nociceptive transmission occurs via C fibers.
B. Distention of a hollow viscus has decreased intensity of pain compared to gut transection.
C. Nociceptive transmission occurs with efferent sympathetic nerve fibers.
D. Most gastrointestinal pain is characterized as a dull, aching sensation at the midline.
E. Visceral pain is often associated with abnormal sympathetic activity.

**4. Afferent pain fibers from most abdominal viscera nociceptors travel with sympathetic fibers in which of the following?**

A. Celiac plexus
B. Superior hypogastric plexus
C. Ganglion impar
D. Stellate ganglion
E. Hepatic plexus

**5. All of the following statements are true regarding ascending pain pathways except:**

A. All first-order afferent nerve fibers enter the spinal cord via the dorsal spinal root.
B. First-order neurons may synapse with sympathetic neurons.
C. Second-order neurons in the dorsal horn mostly decussate to the contralateral side.

D. Wide dynamic range (WDR) neurons are second-order neurons.
E. Third-order neurons are located in the thalamus and send nerve fibers to the cortex.

**6. Which of the following are excitatory neurotransmitters that modulate pain?**

A. Substance P, glutamate, aspartate, γ-aminobutyric acid (GABA)
B. Substance P, glutamate, enkephalins, serotonin
C. Glutamate, aspartate, substance P, adenosine triphosphate (ATP)
D. Glutamate, serotonin, GABA, enkephalins
E. GABA, enkephalins, serotonin, ATP

**7. Release of substance P may cause all of the following except:**

A. Sensitization of nociceptors
B. Vasoconstriction
C. Enhanced chemotaxis
D. Mast cell degranulation
E. Increased neurokinin-1 activity

**8. All of the following statements correctly characterize GABA activity except:**

A. GABA is similar to glycine in that both are inhibitory neurotransmitters that inhibit ascending pain pathways.
B. Inhibition of pain signal transmission is facilitated by $GABA_B$ receptor activity.
C. GABA is an antagonist for *N*-methyl-D-aspartate (NMDA) receptors.
D. Benzodiazepines act on $GABA_A$ receptors.
E. All of the above statements are true.

**9. Which of the following statements is true regarding WDR neurons compared to second-order nociceptive-specific neurons?**

A. WDR neurons have smaller receptive fields compared to nociceptive-specific neurons.
B. WDR neurons are more prevalent than nociceptive-specific neurons.
C. WDR neurons decrease their firing rate with repeated stimulation.
D. WDR neurons only respond to noxious input.
E. Nociceptive-specific neurons can respond to non-noxious stimuli.

**10. A 37-year-old otherwise healthy male experiences second-degree burns on the right forearm following a house fire. On physical exam, he has intense pain after application of mild heat at the site of injury. This is an example of:**

A. Primary hyperalgesia
B. Secondary hyperalgesia
C. Allodynia
D. Paresthesia
E. Disinhibited pain

**11. The same patient (from Question 10) returns 1 year later in clinic and says that after exposure to cold temperatures, he now experiences burning sensations in areas that were not injured during the house fire. Which of the following statements is incorrect regarding the patient's symptoms and central hypersensitivity?**

A. WDR neurons exhibit a reduction in neural activation thresholds.
B. WDR. neurons have increased frequency of discharge with the same stimuli.
C. Substance P increases sensitization.
D. Nonsteroidal anti-inflammatory drugs (NSAIDs) do not have analgesic action on the spinal cord.
E. NMDA receptor activation increases sensitization.

**12. A 71-year-old man who underwent an exploratory laparotomy for small bowel obstruction 2 weeks ago now experiences increased pain and allodynia at the surgical incision site. What direct role would NSAIDs have on relieving this patient's primary hyperalgesia?**

A. Decrease prostacyclin and prostaglandin release
B. Decrease serotonin release
C. Decrease substance P release
D. Decrease calcitonin gene-related peptide (CGRP) release
E. Decrease all of the above substances

**13. Which of the following statements is true regarding the spinothalamic tract?**

A. The lateral spinothalamic tract projects mainly to the ventral posterolateral nucleus of the thalamus.
B. The lateral spinothalamic tract mediates emotional pain perception.
C. The medial spinothalamic tract carries information regarding intensity and location of pain.
D. The medial spinothalamic tract mediates perceptions of vibration and proprioception.
E. The spinothalamic tract mainly ascends in the gray matter of the spinal cord.

**14. The periaqueductal gray (PAG) produces analgesia by all of the following mechanisms except:**

A. Activation of interneurons in lamina II
B. Release of endogenous opioids
C. Inhibition of first-order neurons
D. Decreased release of substance P
E. All of the above statements are true

**15. A 65-year-old male with intra-abdominal and retroperitoneal masses has persistent left-sided abdominal pain despite noninterventional treatments. His pain was refractory to oral medical therapy as well as intrathecal opioids. He underwent a unilateral percutaneous cervical cordotomy, an ablation procedure of the lateral spinothalamic (neospinothalamic) tract. However, he continues to complain of pain and severe distress following treatment. Which of the following statements is most likely true regarding this patient?**

A. Cordotomies are more effective for relieving central pain rather than peripheral pain syndromes.
B. Ablation procedures such as cordotomies should not be recommended for patients with poor life expectancies.
C. A bilateral cordotomy would have been more effective for this patient.
D. Ablation of the medial spinothalamic (paleospinothalamic) tract could also be considered for this patient.
E. Cordotomies are not effective for reducing nociceptive pain.

**16. Which of the following statements is most likely correct regarding the previous patient's pain (from Question 15)?**

A. Inhibition of descending pain modulating pathways should decrease this patient's pain.
B. Spinothalamic fibers do not project to the PAG in the midbrain.
C. The PAG stimulates ascending pain fibers.
D. All pain fibers decussate to the contralateral spinal cord.
E. Other ascending pain pathways may contribute to this patient's pain.

**17. A 58-year-old woman with recently diagnosed postherpetic neuralgia presents to the pain clinic after complaining of persistent hyperesthesia and allodynia. Which of the following best describes the most likely reason for her increased pain?**

A. Decreased glutamate release
B. Activation of NMDA receptors
C. Lack of oral narcotic use
D. Decreased release of GABA
E. Lack of endogenous opiate release

**18. The patient from Question 17 asks you about transcutaneous electrical nerve stimulation (TENS) as an additional modality of treatment for her pain. What is the most likely reason for the efficacy of TENS with relation to the gate control theory?**

A. Inhibition of Aβ nerve fibers
B. Inhibition of the PAG
C. Inhibition of cutaneous nociceptors
D. Inhibition of C pain fibers
E. Inhibition of B fibers

**19. A 49-year-old male with a history of poorly controlled type 2 diabetes mellitus presents to the pain clinic with bilateral lower extremity pain that is described as a constant burning sensation. He would like to avoid any opioid use due to gastrointestinal intolerances. He asks about the possible use of amitriptyline, a tricyclic antidepressant, as an analgesic option. Which of the following would be an appropriate response?**

A. Tricyclic antidepressants would not be helpful because they do not have analgesic properties.
B. Tricyclic antidepressants would not be helpful because they are only effective for nociceptive pain syndromes.
C. Tricyclic antidepressants are adequate alternative analgesics because they predominantly act on μ-opiate receptors.
D. Tricyclic antidepressants are adequate alternative analgesics because they predominantly increase supraspinal inhibition.
E. Tricyclic antidepressants are adequate alternative analgesics because they predominantly act as glycine agonists.

**20. Spinal cord gray matter is composed of 10 layers called Rexed laminae. Aδ fibers synapse predominantly on:**

A. Lamina I and II
B. Lamina I and V
C. Lamina III and IV
D. Lamina VII
E. Lamina II and V

**21. Neurons in Rexed lamina II (substantia gelatinosa) play an important role in modulating pain perception due to:**

A. Inhibitory projections to ascending spinothalamic fibers
B. Increased release of substance P

C. Decreased release of GABA
D. High levels of WDR neurons that increase responsiveness to only noxious stimuli
E. Increased sensitization of cutaneous nociceptors

**22. All of the following are true regarding the actions of endogenous opiates except:**

A. Opioid receptors are distributed widely throughout the central nervous system, including the cerebral cortex, brainstem, dorsal horn, and dorsal root ganglion.
B. PAG stimulation decreases endogenous opiate release.
C. Presynaptic opiate receptor activation inhibits the release of glutamate and substance P.
D. Postsynaptic opiate receptor activation causes neuronal hyperpolarization.
E. Endogenous opiate peptides are antagonized by naloxone.

**23. A 68-year-old male patient with a history of stage IVB hepatocellular carcinoma and diffuse bone metastases whom you have been treating for intractable pain has a pathologic femoral bone fracture. Which of the following systemic responses would you expect to see in this patient?**

A. Tachycardia
B. Hyperglycemia
C. Increased oxygen consumption
D. Hypercoagulability
E. All of the above

## ANSWERS

### 1. ANSWER: E

The vast majority of nociceptors are free nerve endings that respond to noxious stimuli, such as heat, mechanical, and chemical tissue injury. They have high activation thresholds and can increase neural firing rates depending on the intensity of the stimuli. Nociceptors also demonstrate functional plasticity, and with repeated stimulation they have sensitization. This can cause nerve transmission following a low-intensity noxious stimulus (hyperalgesia) or even after a non-noxious stimulus (allodynia). The three major nociceptor types are mechanonociceptors (responsive to pinch and pinprick sensations), silent nociceptors (responsive to inflammation), and polymodal mechano-heat nociceptors (the most common type; responsive to pressure, temperature, and neurochemical mediators such as histamine, capsaicin, and bradykinin).

#### FURTHER READING

Butterworth JF, Mackey DC, Wasnick JD. *Morgan and Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.

### 2. ANSWER: B

Aβ afferent nerve fibers transmit non-noxious stimuli, whereas Aδ and C fibers transmit noxious stimuli (Table 1.1). In general, nerve conduction velocity is dependent on the diameter and degree of myelination of the nerve axon. Myelination increases the electrical insulation of the nerve and conducts the impulse at a higher velocity due to salutatory conduction along the axon. Larger nerves also have improved electrical conduction. As a result, conduction velocities are fastest for large, myelinated A fibers compared to smaller, nonmyelinated C fibers.

*Table 1.1* CHARACTERISTICS OF MAJOR AFFERENT NERVE FIBERS

| | C FIBERS | AΔ FIBERS | AB FIBERS |
|---|---|---|---|
| Function | Diffuse, dull pain | Sharp, localized pain | Light touch |
| Size (diameter; μm) | (0.3–1.6) | (1–4) | (6–22) |
| Myelination | – | + | ++ |
| Conduction velocity (m/s) | <2 | 5–25 | >30 |

#### FURTHER READING

Barash PG, Cullen BF, Stoelting RK, et al. *Clinical Anesthesia*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.

### 3. ANSWER: B

Visceral nociceptors respond to chemical or mechanical stimuli, such as distention, ischemia, and inflammation. They do not respond as intensely to the localized transection or burning associated with surgery. These nerve fibers also synapse at several dermatomal levels and can cross the contralateral dorsal horn. As a result, pain is usually perceived at the midline and is characterized as a nonspecific dull and aching sensation. Visceral afferents travel via unmyelinated C fibers alongside efferent sympathetic nerve fibers. Consequently, afferent activity from these nociceptors is transmitted to the spinal cord between the levels of T1 and L2, and pain can be associated with abnormal sympathetic activity such as nausea, vomiting, and hemodynamic shifts.

#### FURTHER READING

Butterworth JF, Mackey DC, Wasnick JD. *Morgan and Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.

### 4. ANSWER: A

The celiac plexus, which is anterior to the vertebral body of L1, carries afferent nociceptive and sympathetic innervation for most of the abdominal viscera. This includes innervation for the liver, pancreas, biliary tract, gallbladder, adrenal glands, spleen, kidneys, stomach, and small and large bowels. Therefore, celiac plexus blocks are effective for reducing chronic pain from upper abdominal visceral pathology (i.e., intractable pain from pancreatic cancer).

The superior hypogastric plexus, which is located anteriorly to the L5–S2 vertebral bodies, carries afferent and sympathetic innervation for the large bowel distal to the left colonic flexure and the pelvic viscera. The ganglion impar, which is located on the anterior surface of the coccyx, also provides afferent and sympathetic innervation for pelvic viscera. The stellate ganglion, located anteriorly to the C7 vertebral body, carries afferent and sympathetic innervation to portions of ipsilateral head, neck, and arm.

#### FURTHER READING

Kambadakone A, Thabet A, Gervais DA, et al. CT-guided celiac plexus neurolysis: A review of anatomy, indications, technique, and tips for successful treatment. *RadioGraphics*. 2011;31(6):1599–1621.

## 5. ANSWER: A

The transmission of pain signals starts with activation of first-order neurons, which mostly enter the dorsal horn of the spinal cord from the periphery via the dorsal spinal root. A minority of first-order neurons, however, may enter the spinal cord via the ventral nerve root, which is why some patients who undergo rhizotomies (transection of dorsal nerve roots in chronic pain patients for analgesia) can continue to feel pain following the procedure. First-order neurons may travel up or down several spinal segments in Lissauer's tract prior to synapsing with second-order neurons in the dorsal horn, which mostly decussate and cross the midline to the contralateral side of the spinal cord to ascend in the spinothalamic tract. Second-order neurons are either nociceptive-specific or WDR neurons. Both types receive noxious input from Aδ and C fibers, but WDR neurons receive non-noxious input as well. Second-order neurons then synapse with third-order neurons in the thalamus, which send fibers through the internal capsule to the cerebral cortex.

### FURTHER READING


Butterworth JF, Mackey DC, Wasnick JD. *Morgan and Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.

Hemmings HC, Egan TD. *Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application*. Philadelphia, PA: Elsevier; 2013.


## 6. ANSWER: C

There are both excitatory and inhibitory neurotransmitters that act on afferent neurons transmitting pain information (Table 1.2). Substance P is an excitatory neuropeptide released by first-order neurons that acts on neurokinin-1 (NK-1) receptors to facilitate pain transmission. Other important excitatory neurotransmitters are glutamate and aspartate (both act on NMDA receptors), CGRP, and ATP.

*Table 1.2* NEUROTRANSMITTERS IN PAIN MODULATION

| NEUROTRANSMITTER | MODULATING EFFECT |
|---|---|
| Glutamate | Excitatory |
| Aspartate | Excitatory |
| Substance P | Excitatory |
| Calcitonin gene-related peptide (CGRP) | Excitatory |
| Adenosine triphosphate (ATP) | Excitatory |
| γ-Aminobutyric acid (GABA) | Inhibitory |
| Acetylcholine | Inhibitory |
| Enkephalins | Inhibitory |
| β-Endorphins | Inhibitory |
| Serotonin | Inhibitory |
| Norepinephrine | Inhibitory |

### FURTHER READING


Butterworth JF, Mackey DC, Wasnick JD. *Morgan and Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.


## 7. ANSWER: B

Substance P is a neuropeptide that plays a major role as an excitatory neurotransmitter in nociception through its activation of NK-1 receptors. It is synthesized and released in response to painful stimuli from peripheral terminals of sensory nerve fibers and first-order neurons in the dorsal horn. In addition to its role as a facilitator of pain pathways, substance P sensitizes nociceptors, causes histamine degranulation from mast cells, and causes 5-HT release from platelets. Substance P is also a potent vasodilator via its activity on NK-1 receptors on the endothelium of blood vessels.

### FURTHER READING


Butterworth JF, Mackey DC, Wasnick JD. *Morgan and Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.


## 8. ANSWER: C

Both GABA and glycine are important neurotransmitters that are released by inhibitory interneurons in the dorsal horn and have an essential role for inhibiting other excitatory neural pathways. The major neurotransmitter for excitatory interneurons is glutamate. Through inhibition of WDR neurons and ascending pain fibers of the spinothalamic tract in the dorsal horn, G protein-coupled $GABA_B$ receptor activity plays an important role for analgesia. In fact, inhibition of $GABA_B$ receptors can lead to hyperesthesia and allodynia. $GABA_A$ receptors, on the other hand, are ligand-gated ion channels that increase $Cl^-$ influx. Drugs such as benzodiazepines and barbiturates act on these receptors. GABA does not have any inherent NMDA receptor activity.

### FURTHER READING


Butterworth JF, Mackey DC, Wasnick JD. *Morgan and Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.

Hemmings HC, Egan TD. *Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application*. Philadelphia, PA: Elsevier; 2013.

## 9. ANSWER: B

First-order neurons in the ascending pain pathway synapse with either second-order nociceptive-specific neurons or WDR neurons in the dorsal horn. WDR neurons are the most abundant in the dorsal horn. Both nociceptive-specific and WDR neurons receive noxious input from Aδ and C fibers, but WDR neurons receive non-noxious input as well. Therefore, WDR neurons are characterized by large receptive fields, whereas nociceptive-specific neurons have smaller, discrete receptive fields that are normally silent and responsive only to high-threshold noxious input. WDR neurons play a key role in central sensitization of pain. Repeated stimulation can exponentially increase the rate of firing of WDR neurons, causing a "wind-up" phenomenon that leads to increased second-order pain transduction for the same stimulus intensity.

### FURTHER READING

Butterworth JF, Mackey DC, Wasnick JD. *Morgan and Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.
Hemmings HC, Egan TD. *Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application*. Philadelphia, PA: Elsevier; 2013.

## 10. ANSWER: A

This patient is experiencing hyperalgesia, which is an enhanced response to a noxious stimulant (Figure 1.1). Injury to the skin can cause two types: primary and secondary hyperalgesia. Primary hyperalgesia occurs at the site of injury and is due to release of various chemical modulators by the injured tissue (histamine, serotonin, bradykinin, and prostaglandins). This sensitizes nociceptors and decreases the threshold for neural transmission. An enhanced response to the same stimulus intensity can be demonstrated, and continued transmission of pain signals following resolution of the stimulus is also common.

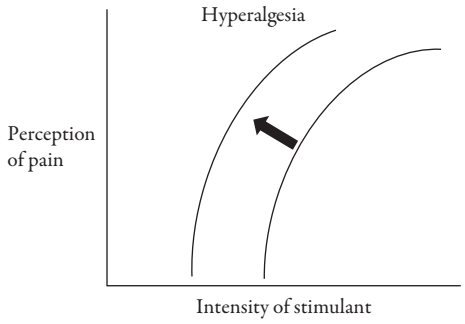


Figure 1.1 Hyperalgesia effect of pain perception.

Secondary hyperalgesia develops in the region immediately surrounding the injured tissue and is a result of substance P release, which causes tissue edema, reddening or flaring of the skin around the site of injury, and sensitization to noxious stimuli. Unlike primary hyperalgesia, which occurs in response to both mechanical and heat stimuli, secondary hyperalgesia is triggered only by mechanical stimuli.

Allodynia refers to perception of pain following a non-noxious stimulant, whereas paresthesia is an abnormal sensation (usually tingling or pricking) without an apparent stimulant.

### FURTHER READING

Butterworth JF, Mackey DC, Wasnick JD. *Morgan and Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.

## 11. ANSWER: D

Central sensitization refers to the enhancement and decreased inhibition of nociceptive pain pathways in the spinal cord to produce pain hypersensitivity. This can occur following an intense noxious stimuli or repeated exposure to stimuli.

Facilitation of central sensitization occurs primarily through one or more of the following mechanisms: (1) sensitization of second-order neurons where WDR neurons have increased response and frequency of discharge following stimulation, (2) a reduction in the neural activation threshold, and (3) an enlargement of the receptor fields such that adjacent neurons in the dorsal horn become responsive to both noxious (hyperalgesia) and innocuous (allodynia) stimuli. This patient is experiencing allodynia in areas beyond the original site of injury.

Substance P is one of the main mediators of central sensitization by facilitating increased neural membrane excitability through its interaction with G protein-coupled membrane receptors. Excitatory amino acids such as glutamate and aspartate also facilitate central sensitization through its activity on NMDA receptors. Prostaglandins help activate the release of these amino acids in the spinal cord; therefore, NSAIDs help reduce central sensitization.

### FURTHER READING

Butterworth JF, Mackey DC, Wasnick JD. *Morgan and Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.

Latremoliere A, Woolf CJ. Central sensitization: A generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10(9):895–926.

Hemmings HC, Egan TD. *Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application*. Philadelphia, PA: Elsevier; 2013.

## 12. ANSWER: A

Tissue injury leads to the release of inflammatory mediators. This includes the production and release of prostaglandins, including prostaglandin $E_2$ ($PGE_2$), which activate and sensitize nociceptors. This leads to decreased nociceptor threshold for firing and an increased response to noxious stimuli as seen with primary hyperalgesia. NSAIDs counteract primary hyperalgesia through the decreased production of prostacyclin and prostaglandins via inhibition of the cyclooxygenase (COX) pathway. Recent studies have also indicated that COX inhibitors may decrease central sensitization of nociception in the spinal cord as well. Neurochemical mediators such as substance P, CGRP, and serotonin all have important excitatory effects on nociception but are not directly affected by NSAIDs.

### FURTHER READING

Sinatra RS, Leon-Cassasola OA de, Viscusi ER. *Acute Pain Management*. New York, NY: Cambridge University Press; 2009.

## 13. ANSWER: A

The spinothalamic tract is the major ascending pain pathway that travels in the anterolateral portion of the spinal cord white matter. Axons of second-order neurons decussate via the anterior white commissure and ascend on the contralateral side to eventually project to supraspinal structures such as the thalamus, nucleus raphe magnus, and periaqueductal gray. Second-order neurons then synapse with third-order neurons in the thalamus to eventually project to the primary somatosensory cortex and the cingulate gyrus. It consists of two main pathways: the medial (paleospinothalamic) and lateral (neospinothalamic) tracts. The neospinothalamic tract transmits information regarding the location, duration, and intensity of pain and communicates to the ventral posterolateral nucleus (VPN) of the thalamus. The paleospinothalamic tract transmits emotional perceptions of pain and communicates to the medial thalamus.

### FURTHER READING

Butterworth JF, Mackey DC, Wasnick JD. *Morgan and Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.

## 14. ANSWER: E

The PAG of the midbrain plays an important role in supraspinal inhibition of ascending pain afferents. Stimulation of the PAG promotes excitatory connections with inhibitory interneurons in Rexed lamina II of the dorsal horn, which release endogenous opioids, such as enkephalin, that bind to μ-opiate receptors on axons of Aδ and C nerve fibers. Opiate receptor activation subsequently decreases substance P release from these primary afferent neurons, thereby inhibiting further activation of ascending second-order neurons and transmission of ascending pain signals. The PAG can also evoke antinociceptive action through adrenergic $\alpha_2$ receptor activation in the dorsal horn. Deep brain stimulation of the PAG has been demonstrated to provide pain relief for some intractable pain syndromes, but it is not widely employed and remains "off-label" in the United States.

### FURTHER READING

Boccard SGJ, Pereira EAC, Aziz TZ. Deep brain stimulation for chronic pain. *J Clin Neurosci*. 2015;22(10):1537–1543.

Budai D, Harasawa I, Fields HL. Midbrain periaqueductal gray (PAG) inhibits nociceptive inputs to sacral dorsal horn nociceptive neurons through $\alpha_2$-adrenergic receptors. *J Neurophysiol*. 1998;80(5):2244–2254.

## 15. ANSWER: D

Patients with malignancies can experience severe pain that is refractory to opiates and intrathecal infusion therapies. Therefore, ablation procedures of the spinothalamic tract can be performed to relieve persistent nociceptive pain, with percutaneous cordotomy being an effective option for those with refractory unilateral nociceptive pain. Although effective at reducing pain, ablation procedures are usually recommended only in patients with limited life expectancies because the analgesic effects diminish over time. It is also more effective at relieving pain from peripheral nociceptor activation as seen with malignant pain syndromes in which tumors infiltrate bones or nerves. Neuropathic and central pain syndromes have less predictable results. Bilateral ablations are not commonly performed and are indicated only for bilateral or midline pain.

Cordotomies typically target ascending pathways in the lateral spinothalamic (neospinothalamic) tract, which

transmits information regarding location, duration, and intensity of pain. Ablations of the medial spinothalamic (paleospinothalamic) tract do not provide analgesia by usual pain metrics, but they can provide relief of distress in malignancy pain syndromes and be helpful for managing the emotional perceptions of pain. Therefore, following an ablation of the paleospinothalamic tract, this patient may continue to perceive pain but not be distressed by it. Note that for this particular question, it is not necessary to know the specifics of what a cordotomy entails. However, one should know the differences between the two major spinothalamic pathways.

## FURTHER READING


Frost EAM. *Clinical Anesthesia in Neurosurgery*. 2nd ed. Boston, MA: Butterworth-Heinemann; 1991.

Tollison CD, Satterthwaite JR, Tollison JW. *Practical Pain Management*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002.


## 16. ANSWER: E

Because there are multiple ascending pain pathways, some patients may continue to perceive pain following ablation procedures of the spinothalamic tract. Like the spinothalamic tract, the spinoreticular tract fibers decussate and ascend in the contralateral spinal cord to transmit signals to the thalamus and hypothalamus. These fibers mediate the emotional and autonomic aspects of pain. The spinocervical tract, another pathway for transmission of nociceptive pain, ascends ipsilaterally to the lateral cervical nucleus and projects to the contralateral thalamus. Dorsal column fibers that travel ipsilaterally and that were traditionally thought to transmit signals for proprioception have also been implicated to transmit visceral nociceptive information.

The PAG in the midbrain and the rostral ventromedial medulla are involved in regulating descending pathways that project to the dorsal horn to inhibit the ascending pain tracts. Therefore, stimulation of these areas with implants has been demonstrated to be potentially helpful in patients with chronic pain. It is important to know that fibers of the spinothalamic tract also project to the PAG and can modulate descending inhibitory pathways.

## FURTHER READING


Butterworth JF, Mackey DC, Wasnick JD. *Morgan and Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.

Frost EAM. *Clinical Anesthesia in Neurosurgery*. 2nd ed. Boston, MA: Butterworth-Heinemann; 1991.

Palecek J, Paleckova V, Willis WD. The roles of pathways in the spinal cord lateral and dorsal funiculi in signaling nociceptive somatic and visceral stimuli in rats. *Pain*. 2002;96(3):297–307.


## 17. ANSWER: B

This patient is experiencing wind-up, a mechanism of central pain sensitization. With repeated activation of C fibers, a progressive increase in the evoked response is seen such that WDR neurons increase their frequency of firing and also have prolonged firing after resolution of the stimulus. Glutamate and aspartate, both excitatory neurotransmitters, are important facilitators for wind-up through their activation of NMDA receptors, which can be found on WDR neurons. NMDA antagonists, such as ketamine, have been found to reduce wind-up pain in patients with postherpetic neuralgia and central neuropathic pain syndromes as well.

## FURTHER READING


Eide PK. Wind-up and the NMDA receptor complex from a clinical perspective. *Eur J Pain*. 2000;4(1):5–15.


## 18. ANSWER: D

TENS is a noninvasive treatment that applies electrical current to the skin. This tactile, non-noxious stimulation activates Aβ fibers and modulates afferent information carried by ascending C pain fibers by inhibition within the substantia gelatinosa (or Rexed lamina II of the dorsal horn). This descending inhibition initiated by Aβ fibers is achieved via stimulation of the PAG. This has often been referred to as the gate control theory of pain. TENS has been associated with improving pain symptoms and decreasing opiate requirements in neuropathic pain syndromes, including postherpetic neuralgia, as well as in other acute pain syndromes.

## FURTHER READING


Breivik H, Campbell WI, Nicholas MK. *Clinical Pain Management: Practice and Procedures*. 2nd ed. Boca Raton, FL: CRC Press; 2008.


## 19. ANSWER: D

Unlike nociceptive pain syndromes, chronic neuropathic pain syndromes are due to primary damage to nerve fibers

of the peripheral or central nervous system. These conditions can be difficult to treat with conventional analgesics such as opiates and NSAIDs alone. Antidepressants such as tricyclic antidepressants (TCAs) and anticonvulsants such as gabapentin or pregabalin are typically considered first-line agents. TCAs inhibit serotonin and catecholamine reuptake in the synaptic nerve cleft, which increases monoamine-mediated inhibition of ascending pain pathways, thereby producing analgesia. This patient is experiencing diabetic neuropathic pain from his poorly controlled disease and would be considered an excellent candidate for antidepressant therapy.

## FURTHER READING

Moore RA, Derry S, Aldington D, et al. Amitriptyline for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2015;7:CD008242.

## 20. ANSWER: B

The spinal cord gray matter is divided into 10 Rexed laminae (Table 1.3), which follow a topographic organization and are organized based on different functions. Laminae I–VI comprise the dorsal horn and serve as the major area where both ascending and descending spinal pathways modulate pain. Some of the important layers are discussed here.

*Table 1.3* REXED LAMINAE FUNCTIONS

| REXED LAMINAE | FUNCTIONS |
|---|---|
| I | Somatic nociception, thermoreception |
| II | Somatic nociception, thermoreception, opiate responsive |
| III | Mechanoreception, proprioception |
| IV | Mechanoreception, proprioception |
| V | Visceral, somatic nociception, mechanoreception |
| VI | Mechanoreception, proprioception |
| VII | Preganglionic sympathies |
| VIII | Anterior motor horn |
| IX | Anterior motor horn |
| X | Central gray commissures |

Lamina I contains second-order neurons that receive cutaneous and deep somatic nociceptive pain and temperature afferents. Lamina II (or substantia gelatinosa) contains second-order neurons that modulate cutaneous nociceptive information and are opiate responsive. Lamina III and IV second-order neurons receive non-nociceptive input and relay information regarding touch and proprioception. Lamina V processes visceral and somatic pain as well as non-noxious afferent information. Lamina VI relays proprioception information. Lamina VII contains preganglionic sympathetic neurons. Lamina VIII and IX comprise the anterior motor horn. Nociceptive C fibers synapse predominantly with second-order neurons in laminae I and II, whereas Aδ fibers terminate mainly on laminae I and V.

## FURTHER READING

Butterworth JF, Mackey DC, Wasnick JD. *Morgan and Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.
McMahon SB, Koltzenburg M, Tracey I, et al. *Wall and Melzack's Textbook of Pain*. 6th ed. Philadelphia, PA: Elsevier, 2013.

## 21. ANSWER: A

Rexed lamina II (substantia gelatinosa) neurons receive input from both Aδ and C fibers and play an essential role in modulating spinothalamic nerve fibers through their inhibitory interneurons. They do not release substance P. Lamina II interneurons also play an important role in analgesia through their expression of μ-opioid receptors. Although WDR neurons are common in the dorsal horn, they are most prevalent in lamina V. These second-order neurons have excitatory projections and respond to both non-noxious and noxious stimuli.

## FURTHER READING

Trafton JA, Abbadie C, Marek K, et al. Postsynaptic signaling via the [mu] opioid receptor: Responses of dorsal horn neurons to exogenous opioids and noxious stimulation. *J Neurosci*. 2000;20(23):8578–8584.

## 22. ANSWER: B

The endogenous opiate system consists of three main peptides (β-endorphin, enkephalins, and dynorphins) and three main G protein-coupled receptors (μ, δ, and κ), which are widely expressed in the central nervous system, including the cerebral cortex, brainstem, limbic system, dorsal horn, and dorsal root ganglion. The release of endogenous opiates is triggered by activation of the PAG. Activation of opioid receptors leads to presynaptic inhibition of the release of excitatory chemical neurotransmitters, such as glutamate, substance P, and CGRP. Concurrently, opioid receptor activation also causes postsynaptic hyperpolarization for decreased neuronal excitability. Exogenous opioids

have a predilection to act on second-order neurons in the substantia gelatinosa of the spinal cord. Both endogenous and exogenous opiates are antagonized by naloxone.

## FURTHER READING

Benarroch EE. Endogenous opioid systems: Current concepts and clinical correlations. *Neurology*. 2012;79(8):807–814.

### 23. ANSWER: E

A neuroendocrine stress response is seen with acute pain syndromes that can be attributed to increased sympathetic activation and release of stress hormones. It can also be witnessed in chronic pain patients who experience prominent recurring nociceptive and central pain syndromes. Common cardiovascular effects include hypertension and tachycardia, which lead to increased cardiac output for patients with preserved cardiac function. This may also lead to increased oxygen consumption with increased work of breathing. An increase in the release of catecholamines and cortisol additionally leads to hyperglycemia as well as stress-related immunosuppression. Increased sympathetic activity can cause urinary retention or ileus. Hypercoagulability can also be seen with decreased fibrinolytic states. The patient described in this question is experiencing severe acute, superimposed on chronic pain, which places him at a high likelihood of developing the described systemic stress response.

## FURTHER READING

Barash PG, Cullen BF, Stoelting RK, et al. *Clinical Anesthesia*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.

Butterworth JF, Mackey DC, Wasnick JD. *Morgan and Mikhail's Clinical Anesthesiology*. 5th ed. New York, NY: McGraw-Hill; 2013.

Hemmings HC, Egan TD. *Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application*. Philadelphia, PA: Elsevier; 2013.

# 2.

# LITERATURE REVIEW AND EVIDENCE

*Andrea L. Nicol and Usman Latif*

## INTRODUCTION

This chapter reviews concepts underlying critical analysis of literature and evidence-based medicine because a thorough understanding of these topics is of utmost importance in the interpretation of medical literature and applicability of the results therein. Basic principles of valid clinical research and components of clinical trials are reviewed. The chapter explores specific topics pertaining to the designing, reporting, and interpreting of clinical studies about the treatment of pain. The effects of the analysis on the clinical applicability of study results are also discussed. Finally, the chapter identifies special features specific to the study of pain.

## QUESTIONS

**1. An investigator is performing a study in which there will be 100 separate independent comparisons in the analysis. At a significance level of 0.05, how many false-positive findings are possible on the average based on chance alone?**

A. 1
B. 5
C. 10
D. 25
E. 100

**2. Which of the following is false regarding levels of evidence?**

A. Evidence meeting the highest standard is rated 1a.
B. An individual randomized control trial (RCT) with a narrow confidence interval (CI) is rated as the highest level of evidence possible.
C. An expert opinion is rated as a lower level of evidence than a case series.
D. A common standard for levels of evidence allows for a uniform approach to comparison of different sources of data.
E. Ratings are based on the design and quality of the study or paper.

**3. Which of the following components of study design eliminates confounding by baseline variables, removes investigator bias, and guarantees that statistical tests will have valid false-positive error rates?**

A. Blinding
B. Sample size calculation
C. Informed consent
D. Randomization
E. Effect size

**4. A researcher is interested in performing a randomized placebo-controlled trial for patients undergoing lumbar transforaminal steroid injections. Which of the following study parameters poses the greatest ethical challenge in the development and design of the proposed study?**

A. Placebo control
B. Blinding
C. Sample size
D. Inclusion criteria
E. Interim analysis

**5. Which of the following is not an element of an informed consent?**

A. A statement that participation is voluntary
B. A description of the benefits to the subject or others expected from the research
C. Contact information for the US Department of Health and Human Services

D. A description of the foreseeable risks and discomforts to the subject
E. The expected duration of the subject's participation

**6. Which of the following is true regarding grades of recommendation?**

A. Grades of recommendation are used to describe the quality of the collection of evidence supporting an assertion using a range of 1 to 5.
B. Grades range from A to D.
C. 1a is the highest grade of recommendation.
D. Whether a recommendation is based on extrapolation is irrelevant to grading.
E. Grades of recommendation are ordered from lowest to highest levels of evidence strength.

**7. Which of the following scales or questionnaires would be most beneficial to a pain researcher who is interested in measuring physical functioning as a marker of health-related quality of life in a study of patients with chronic low back pain?**

A. Visual numerical pain score
B. Short Form (SF)-36
C. Visual analogue pain score
D. McGill Pain Questionnaire
E. Brief Pain Inventory

**8. A study was performed to evaluate the efficacy of a new neuropathic drug in the treatment of postherpetic neuralgia. In the initial phase, all patients received the study drug, and outcome measures for changes in visual numerical pain scores were assessed before and after the study period. After the study period was complete, the researchers analyzed the data and selected only those patients who responded with a 30% or greater reduction in pain to continue the study in a randomized placebo-controlled trial. What specific type of study design is described here?**

A. Crossover study design
B. Retrospective study design
C. Enrichment design
D. N-of-1 study design
E. Adaptive study design

**9. An RCT study design is more likely to result in all of the following except:**

A. Unbiased distribution of confounders
B. Facilitation of statistical analysis
C. Increased expense
D. Decreased volunteer bias
E. Attrition bias based on group allocation

**10. Which of the following parameters provides clinicians with information on both the clinical significance and the statistical significance of an inferential statistical test?**

A. *p* value
B. Effect size
C. Standard deviation
D. Confidence interval
E. Sample size

**11. Which of the following is not a core outcome domain for chronic pain clinical trials as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)?**

A. Symptoms and adverse events
B. Physical functioning
C. Emotional functioning
D. Ratings of global improvement
E. Health care utilization

**12. All the following are factors that should be considered when deciding whether you should use a parametric or nonparametric statistical analysis approach except:**

A. The shape of the data distribution
B. The type of the data being analyzed
C. The assumption that samples are independent
D. The type of study design used
E. The assumption that variances are homogeneous

**13. Match the following terms to the statements:**

- **Case–control study**
- **Cross-sectional survey**
- **Crossover design**
- **Randomized controlled trial**
- **Cohort study**

A. What is a controlled trial in which each subject has both therapies at various points in time?
B. What design is best for studying the effect of an intervention?
C. What is a study design in which data are obtained from groups who have been exposed or not exposed to a variable of interest?
D. Which study design is best for the study of the effect of predictive risk factors on an outcome?
E. The prevalence of a disease or risk factor can be quantified best with which study design?
F. What is the only feasible study design for the study of very rare disorders?

**14. A clinical trial is performed to evaluate the effectiveness of a new drug for fibromyalgia in a population sample of 120 patients. The mean decrease in pain scores after treatment in the active treatment group is 4.5. The mean decrease in average pain scores after treatment in the placebo group is 2.8. Assuming a normal distribution of the data, which statistical test is the best to utilize in comparing the mean change in average pain scores between the two groups?**

A. Analysis of variance (ANOVA)
B. Student's *t*-test
C. Wilcoxon rank-sum test
D. Pearson coefficient of correlation
E. Chi-square test

**15. Which of the following was developed as a tool to facilitate the complete and transparent reporting of trials and aid in their critical appraisal and interpretation in response to suboptimal and inadequate reporting of results from randomized controlled trials?**

A. Cochrane database
B. PubMed
C. Consolidated Standards of Reporting Trials (CONSORT) Statement
D. Meta-analysis
E. EMBASE

**16. What magnitude of change in visual analogue scale pain score is reported to be consistent with at least a moderately clinically meaningful reduction to chronic pain patients?**

A. ≥20%
B. ≥30%
C. ≥40%
D. ≥50%
E. ≥60%

**17. Which statistical principle is defined by the inclusion of all patients for analysis in the groups to which they were assigned, regardless of protocol adherence?**

A. Intention-to-treat
B. Crossover
C. Per protocol
D. Bootstrapping
E. Subgroup analysis

**18. Which of the following could be classified as an ordinal variable?**

A. Color of eyes
B. Temperature (Celsius)
C. Satisfaction rating (very satisfied, moderately satisfied, etc.)
D. Height (cm)
E. Gender (male or female)

**19. All of the following statements about research characteristics are true except:**

A. In a double-blinded study, both patients and providers are unaware of the patients' group assignment.
B. Randomization is a process of selecting from a group in a manner that makes equal distribution of confounders likely.
C. If the patients who are likely to volunteer for a study are different than the general population, that is an example of confounding.
D. Stratification is a strategy in which patients are intentionally divided by an important characteristic prior to randomization.
E. In a triple-blinded study, patients, providers, and another group (e.g., data analyzers or support staff) are unaware of the patients' group assignment.

**20. Which of the following is the probability of failing to reject the null hypothesis when there is an association between predictor and outcome?**

A. Power
B. *p* value
C. Effect size
D. $\alpha$
E. $\beta$

**21. An investigator is researching the efficacy of two different drugs for painful diabetic polyneuropathy. In the study, there are two separate treatment periods separated by a period of time in which they are administered no medication. In the first treatment period, half of the group will be administered drug A and half will be administered drug B. In the second treatment period, the groups will receive the drug they did not receive in the first treatment period. What type of study design has this investigator employed for his research?**

A. Crossover
B. Enrichment
C. Dose-finding
D. Randomized controlled trial
E. Adaptive

**22. Which of the following groups of people are not considered to be vulnerable populations in research as**

**defined by the US Department of Health and Human Services?**

A. Children and minors
B. Cognitively impaired persons
C. Cancer patients
D. Pregnant women
E. Prisoners

**23. All of the following parameters are required to calculate sample size except:**

A. Effect size
B. Variability (standard deviation)
C. $\alpha$
D. $\beta$
E. *p* value

**24. Which of the following components of clinical trial design specifies and defines the main characteristics of the sample population relevant to the research question?**

A. Sample size
B. Inclusion criteria
C. Recruitment
D. Sampling error
E. Internal validity

**25. Match the following terms to the statements:**

- **Positive predictive value**
- **Number needed to treat (NNT)**
- **Power**
- **Specificity**
- **Sensitivity**

A. The inverse of the absolute risk reduction (ARR) is equal to which measure?
B. Which measure correlates with the proportion of negatives that are correctly identified as such?
C. The number of true positives divided by the sum of true positives and false positives is equal to?
D. Which measure quantifies the likelihood of identifying a significant effect when it exists?

## ANSWERS

### 1. ANSWER: B

Many clinical trials have more than one measured outcome variable and several demographic variables of interest. Thus, a number of statistical comparisons will need to be made to analyze and interpret all of the data. The issue of multiple comparisons arises when enough significance tests are done, which leads to the increased likelihood that a test will be statistically significant based on chance alone. Multiple comparisons include repeated analyses of the same outcome variable and comparisons of multiple variables, including testing for differences in baseline characteristics and subgroup analyses. The significance level is also known as the type I error rate and is the probability of a false positive. It is denoted by the Greek letter $\alpha$.

The implication of multiple comparisons is that the investigator should be cautious when interpreting the results. One way to counter the problem is to require a lower significance level; however, this will reduce the power of the trial. Another alternative is to increase the sample size so that a smaller significance level can be used while maintaining the power of the trial. This option may prove to be quite difficult for most investigators. Many adjustments can be used to approximate or control the significance level that should be used for interpretation of significant findings, including the Bonferroni correction, Holm procedure, and Hochberg procedure.

In the case of this investigator who is running 100 separate comparisons with a significance level of 0.05, 5 of them will be significant based on chance alone.

### FURTHER READING


Cook TD, DeMets DL. Selected issues in the analysis. In: *Introduction to Statistical Methods for Clinical Trials*. Boca Raton, FL: Chapman & Hall/CRC Press; 2008: 333–370.

Friedman LM, Furberg CD, DeMets DL. Issues in data analysis. In: *Fundamentals of Clinical Trials*. 4th ed. New York, NY: Springer; 2010:345–390.


### 2. ANSWER: B

Utilizing a common framework for judging the strength of scientific work allows for a standard approach to comparing evidence and allows conflicting evidence to be weighted differentially. This systematic approach to levels of evidence is essential to the practice of evidence-based medicine. The Oxford Centre for Evidence-Based Medicine publishes and maintains a "Levels of Evidence" document.

Evidence is classified into one of five categories (Box 2.1). The evidence is then rated, in declining order of strength, as 1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, or 5. The ratings are based on the design and quality of the study or paper. For example, for therapy studies, systematic reviews (with homogeneity) of RCTs receive the highest rating of 1a. Cohort studies and outcomes research generally receive a rating in the 2 category, whereas case–control studies are classified in the 3 category. A case series would be rated as 4, whereas an expert opinion paper would receive the lowest rating of 5.

*Box 2.1* EVIDENCE CATEGORIES

**Therapy/Prevention or Etiology/Harm**

**Prognosis**

**Diagnosis**

**Differential Diagnosis or Symptom Prevalence Study**

**Economic and Decision Analysis**

### FURTHER READING


Centre for Evidenced-Based Medicine (CEBM). Oxford Centre for Evidence-Based Medicine—Levels of evidence (March 2009). 2009. Available at http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009. Accessed July 21, 2015.


### 3. ANSWER: D

Randomized control trials are comparative studies with an intervention group and a control group, in which the assignment of a subject to a group is determined by a formal process of randomization. In the simplest of terms, randomization is a procedure in which all participants are equally likely to be assigned to either the intervention group or the control group.

Randomization is an important concept and is advantageous for many reasons. First, randomization tends to produce comparable groups. This means that measured and unmeasured or unknown characteristics and prognostic factors of the participants will be, on average, evenly balanced between the intervention and control groups. Second, randomization removes the possibility of bias in the allocation of participants to the intervention group or to the control group, also known as selection bias. Selection bias can be conscious or subconscious and can easily invalidate comparisons, which is why randomization is so important. Finally, randomization provides a sound foundation for valid statistical inference and guarantees the validity of inferential tests of statistical significance. Thus, it ensures independence between assigned treatment and outcome and allows the researcher to state that observed differences between treatment groups are not attributable to chance.

Many different procedures can be employed to provide randomization for research studies, including blocked, stratified, adaptive, and play the winner.

## FURTHER READING


Cook TD, DeMets DL. Randomization. In: *Introduction to Statistical Methods for Clinical Trials*. Boca Raton, FL: Taylor & Francis; 2008:141–170.

Friedman LM, Furberg CD, DeMets DL. Issues in data analysis. In: *Fundamentals of Clinical Trials*. 4th ed. New York, NY: Springer; 2010:345–390.

Piantadosi S. Treatment allocation. In: *Clinical Trials: A Methodologic Perspective*. 2nd ed. Hoboken, NJ: Wiley; 2005:331–353.


## 4. ANSWER: A

Although randomized, placebo-controlled trials are highly regarded to be the gold standard of clinical research, the use of a placebo in surgery and skill-dependent therapies, such as interventional pain management, is considered to be controversial due to the ethical considerations of performing a "sham" intervention. Sham interventions are apt to cause moral discomfort in clinician–investigators, who are trained to perform invasive interventions only for the medical benefit of patients.

Although sham interventions have the potential to harm subjects, research designs without a placebo or sham intervention are considered to be scientifically less vigorous. Horng and Miller contend that ethical objections—based on risk–benefit optimization and informed consent issues—do not support an absolute prohibition of the use of placebo/sham interventions when their use is methodologically necessary to answer clinically relevant questions. They suggest that each proposed trial involving sham procedures must be carefully evaluated in light of these ethical considerations. Furthermore, Miller and Kaptchuk purport that the use of sham interventions does not violate the rights of patient–subjects provided they have been adequately informed and fully understand that they will receive either a real or a sham intervention.

## FURTHER READING


Horng S, Miller FG. Is placebo surgery unethical? *N Engl J Med*. 2002;347:137–139.

Miller FG, Kaptchuk TJ. Sham procedures and the ethics of clinical trials. *J R Soc Med*. 2004;97(12):576–578.

Piantadosi S. Contexts for clinical trials. In: *Clinical Trials: A Methodologic Perspective*. 2nd ed. Hoboken, NJ: Wiley; 2005:65–105.


## 5. ANSWER: C

Informed consent is an essential and important facet of clinical research. Instead of being viewed as a simple endpoint of a signature on a form, the consent document should be viewed as a basis for meaningful exchange of information between the investigator and the subject. Institutional review boards (IRBs), clinical investigators, and research sponsors all share responsibility to ensure that the informed consent process is adequate. The US Food and Drug Administration's *Code of Federal Regulations* Title 21 provides the required basic and optional additional elements of the informed consent document (Box 2.2).

### *Box 2.2* BASIC AND ADDITIONAL ELEMENTS OF INFORMED CONSENT

- Basic elements
  - A statement that the study involves research, including
    - Explanation of the purposes of the research
    - Expected duration of the subject's participation
    - Description of the procedures to be followed
    - Identification of experimental procedures
  - Description of reasonable foreseeable risks or discomforts to the subject
  - Description of any benefits to the subject or others that may be expected from the research
  - Disclosure of alternative procedures or treatment that may be advantageous to the subject
  - A statement describing how confidentiality of the records identifying the subject will be maintained
  - For research involving more than minimal risk
    - Explanation as to whether compensation and any medical treatments are available if injury occurs *and*
    - If so, what they consist of and where further information can be obtained
  - Contact information for answers to pertinent questions about the research and research subject's rights and whom to contact in the event of a research-related injury
  - A statement that participation is voluntary
    - Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled
    - Subject may discontinue participation at any time without penalty
- Additional elements
  - A statement that there may be unforeseeable risks to the subject
  - Circumstances in which the subject's participation may be terminated by the investigator
  - Any additional costs to the subject that may result from participation in the research
  - Consequences of a subject's decision to withdraw from the research
    - Procedures for orderly termination of participation by the subject
  - A statement that significant new findings developed during the course of research that may relate to their willingness to continue participation will be provided
  - The approximate number of subjects involved in the study

## FURTHER READING

US Department of Health and Human Services, Office for Human Research Protections. Informed consent checklist. Available at http://www.hhs.gov/ohrp/policy/consentckls.html. Accessed July 10, 2015.

US Food and Drug Administration. A guide to informed consent—Information sheet. Available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm. Accessed July 10, 2015.

US Food and Drug Administration. CFR—Code of Federal Regulations Title 21. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25. Accessed July 10, 2015.

## 6. ANSWER: B

When making an evidence-based recommendation, it is important to be able to summarize the quality of the underlying evidence. The Oxford Centre for Evidence-Based Medicine has designed a system for grading recommendations. Grades of recommendation range, in declining order of strength of underlying evidence, from A to D. The grading takes into account the levels of evidence assigned to the underlying studies. Also taken into account is whether extrapolation has occurred or whether the intended use situation has potential clinically important differences from the original study situation. This type of extrapolation generally results in a one category downgrade of the grade of recommendation. The Oxford Centre for Evidence-Based Medicine has summarized this grading scale (Table 2.1).

*Table 2.1* **GRADES OF RECOMMENDATION**

| GRADE | DESCRIPTION |
|---|---|
| A | **Consistent level 1 studies** |
| B | **Consistent level 2 or 3 studies *or* extrapolations from level 1 studies** |
| C | **Level 4 studies *or* extrapolations from level 2 or 3 studies** |
| D | **Level 5 evidence *or* troublingly inconsistent/inconclusive studies of any level** |

## FURTHER READING

Centre for Evidenced-Based Medicine (CEBM). Oxford Centre for Evidence-Based Medicine—Levels of evidence (March 2009). 2009. Available at http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009. Accessed July 21, 2015.

## 7. ANSWER: E

In a clinical trial for chronic pain, pain reduction is a necessary outcome variable; however, it is important to consider other outcomes in clinical trials. In order to relieve clinical symptoms, the objectives of health care interventions include improvement of functioning and health-related quality of life. IMMPACT was formed with the mission to develop consensus reviews and recommendations for improving the design, execution, and interpretation of clinical trials for treatments of pain. IMMPACT recommendations and guidelines have been widely cited and have helped guide clinical trial design. Specific areas in which they have made recommendations include core outcome domains, core outcome measures, development of outcome measures, interpretation of clinical importance of treatment outcomes, core outcome and treatment measures for pediatric pain, clinical importance of group differences, analyzing multiple endpoints, research design for confirmatory clinical trials, research design for proof-of-concept studies, and design implications for chronic pain prevention studies.

With regard to the physical functioning domain of health-related quality of life, measures include the ability to carry out such daily activities as household chores, walking, work, travel, and self-care, in addition to strength and endurance measures. Based on the 2005 IMMPACT consensus publication, the group recommends use of either the Multidimensional Pain Inventory or the Brief Pain Inventory (BPI) for physical functioning measures. The BPI contains a Pain Interference Scale that provides reliable and valid measures of the interference of pain with physical functioning. The SF-36 Health Survey may be used as a more generic measure of health-related quality of life per IMMPACT's guidelines.

## FURTHER READING

Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113:9–19.

Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT). IMMPACT website. http://www.immpact.org/index.html. Accessed July 13, 2015.

## 8. ANSWER: C

Treatment response is often highly variable among subjects in clinical trials for pain. Variability may be due to multiple factors, including different degrees of improvement due to placebo effects or other nonspecific factors, protocol adherence, difficulty in reliable and consistent pain reporting, difficulty tolerating the treatment, and treatments working better in some individuals than in others. The enrichment study design can be used in an attempt to decrease these various sources of variability in order to increase the chances of detecting an effect if it truly exists. An enrichment design uses run-in periods to identify and exclude

subjects who have a prespecified level of treatment or placebo response, noncompliance, treatment intolerability, or variability in pain ratings. Thus, the enrichment design helps a researcher select subjects in whom a treatment effect may be more easily detected.

In the case of this study, by enriching the study with subjects based on a prespecified level of positive response to the investigational treatment, the second phase of the study will consist of a cohort of subjects for whom the treatment is likely to be efficacious. Limitations of enrichment study design include a limit on the generalizability of the results to a larger population of patients and the possibility of unblinding in the second phase as a patient who responds to a certain treatment may recognize the absence of pain relief or side effects if he or she is switched to placebo.

## FURTHER READING


Dworkin RH, Turk DC, Peirce-Sandner S, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2010;149:177–193.

Gewandter JS, Dworkin RH, Turk DC, et al. Research designs for proof-of-concept chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2014;155:1683–1695.


## 9. ANSWER: D

Randomized controlled trials are experimental studies in which subjects are randomly assigned to treatment/intervention groups or control/placebo groups. RCTs are among the most rigorous study designs that can be employed. The advantages of such a design include increased likelihood of blinding (particularly in double-blinded studies), statistical analysis facilitated by randomization, and unbiased distribution of confounders.

The disadvantages include increased time to conduct the research; increased expense; and occasionally ethical ramifications having to do with randomizing patients to different treatment or nontreatment/placebo groups, especially if there is concern that one treatment option may be clearly superior. Attrition bias may occur when patients drop out of the study from one or the other of the study groups preferentially. For example, participants in the control group may be unhappy with a lack of progress and may drop out of the study to seek alternative treatment or participants in the treatment group may become lost to follow-up if treatment has been successful.

An additional disadvantage is volunteer bias. The goal of sampling is to obtain a representative sample of the larger population to be studied. Randomization is employed to improve the quality of the sample. However, patients are being randomized from a sample population consisting of volunteers willing to participate in the research. It may be possible that the individuals who are willing to volunteer for research are different in characteristics than the population as a whole. For example, it may be that more impoverished individuals volunteer for a paid drug trial, whereas affluent individuals do not.

## FURTHER READING


Centre for Evidence-Based Medicine (CEBM). Study designs. 2014. Available at http://www.cebm.net/study-designs. Accessed July 21, 2015.

University of Texas at Austin. Common mistakes in using statistics: Biased sampling. 2015. Available at http://www.ma.utexas.edu/users/mks/statmistakes/biasedsampling.html. Accessed July 21, 2015.


## 10. ANSWER: D

The main purpose of clinical research is to perform a study in which the results obtained are applicable to a target population of people with a certain disease. Practically speaking, it is usually not possible to perform a study on "all" people in the target population. Instead, studies are performed on a sample of people drawn from the target population. The results of a clinical study are therefore used as estimates of what may happen if the treatment is given to the whole population of interest. Confidence intervals (CIs) provide a range of plausible values for a population parameter based on the study data results and give an indication of the precision of the measured treatment. The 95% CI is usually reported in the medical literature and represents the range in which there is 95% certainty that the true population parameter will lie. The width of a CI indicates the precision of the estimated parameter in that the wider the CI, the less the precision and higher amount of random error in the measurements.

CIs also provide useful information on the clinical importance of the results and, like *p* values, can be used to assess statistical significance. Clinical significance is represented by a difference in effect size between groups that could be considered important in clinical decision-making. If an effect size is known as being clinical important, CIs that contain that effect size values can indicate that the result of the test is likely of clinical significance. *p* values provide no information on the clinical importance of any observed differences between study groups. Whereas a *p* value indicates whether the results could or could not have arisen by chance, a statistically significant finding has little relation to clinical significance. CIs can provide information on statistical significance in that a *p* value will be less than 0.05 if the CI does not include whatever value is specified in the null hypothesis. For example, if a CI for a mean difference does not include 0,

the data are not consistent with equal population means, and we can state that there is a statistically significant difference between the groups.

## FURTHER READING


Akobeng AK. Confidence intervals and *p*-values in clinical decision making. *Acta Paediatr*. 2008;97:1004–1007.

Gardner MJ, Altman DG. Confidence intervals rather than *P* values: Estimation rather than hypothesis testing. *Br Med J (Clin Res Ed)*. 1986;292:746–750.


## 11. ANSWER: E

IMMPACT was formed with the mission to develop consensus reviews and recommendations for improving the design, execution, and interpretation of clinical trials for treatments of pain. IMMPACT recommendations and guidelines have been widely cited and have helped guide chronic pain clinical trial design. Specific areas in which it has made recommendations include core outcome domains, core outcome measures, development of outcome measures, interpretation of clinical importance of treatment outcomes, core outcome and treatment measures for pediatric pain, clinical importance of group differences, analyzing multiple endpoints, research design for confirmatory clinical trials, research design for proof-of-concept studies, and design implications for chronic pain prevention studies.

Turk et al. recommended that each of the six core outcome domains should be considered in all clinical trial designs for both efficacy and effectiveness of treatments for chronic pain. Furthermore, if one or more of the domains are not used as an outcome in a study, the reasons for excluding the outcome should be justified a priori. The six core outcome domains as recommended by IMMPACT are pain, physical functioning, emotional functioning, participant ratings of global improvement and satisfaction with treatment, symptoms and adverse events, and participant disposition. Additional or supplemental outcome domains that researchers may elect to use include role functioning, interpersonal functioning, pharmacoeconomic measures and health care utilization, biological markers, coping, clinician ratings of global improvement, neuropsychological assessments of cognitive and motor function, and suffering or other end-of-life issues.

## FURTHER READING


Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. IMMPACT website. http://www.immpact.org/index.html. Accessed July 13, 2015.

Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2003;106(3):337–345.


## 12. ANSWER: D

Parametric and nonparametric are two broad classifications of statistical testing procedures. Parametric tests are based on assumptions about the distribution of the underlying population from which the sample was taken. The most common assumption is that the data are normally distributed, also known as a Gaussian distribution. Characteristics of normal distributions include the following : Data are symmetric about the mean, have bell-shaped density curves with a single peak, and are defined by mean ($\mu$) and standard deviation ($\sigma$); and mean, median, and mode are the same. In normal distributions, 68% of the total area under the curve is within one standard deviation of the mean, 95% of the total area under the curve is within two standard deviations of the mean, and 99.7% of the total area under the curve is within three standard deviations of the mean. Other factors that determine whether or not a parametric test is suitable include the type of data being analyzed, homogeneity of variances, and whether or not the samples are independent. In contrast, nonparametric statistical procedures rely on few or no assumptions about the shape or parameters of the population distribution from which the sample was taken.

It is important to understand when to use a parametric versus a nonparametric statistical procedure. Nonparametric tests use less information and therefore are more conservative tests compared to their parametric alternatives. Thus, if a nonparametric test is used when you have parametric data, the power of the analysis can be decreased, meaning you are less likely to get a significant result when there truly is a significant result. However, if a parametric test is used wrongly when the data are actually nonparametric, the likelihood of incorrect conclusions increases. In addition to less power, results of nonparametric procedures are more difficult to interpret because many of the tests use rankings of the values in the data rather than using the actual data, which reduces the clinical understanding of the data and results.

## FURTHER READING


Hoskin T. Parametric and nonparametric: Demystifying the terms. Available at http://www.mayo.edu/mayo-edu-docs/center-for-translational-science-activities-documents/berd-5-6.pdf. Accessed July 23, 2015.

## 13. ANSWERS:

A. A controlled trial in which each subject has both therapies at various points in time is a crossover design. Studies with a crossover design allow each subject to receive both therapies. They are randomized to treatment A or treatment B first and then switch to the other treatment at the crossover point. Subjects serve as their own controls, and all subjects receive treatment at least part of the time. This design can be problematic if the washout period for a treatment is lengthy or unknown. In addition, the treatment effect has to be reversible. In other words, if the treatment could lead to a permanent cure for a condition, then a crossover study design is not appropriate.

B. The design that is best for studying the effect of an intervention is the randomized controlled trial. See "randomized controlled trial" row in Table 2.2.

C. The study design in which data are obtained from groups that have been exposed or not exposed to a variable of interest is a cohort study. See "cohort study" row in Table 2.2.

D. The study design that is best for the study of the effect of predictive risk factors on an outcome is a cohort study. See "cohort study" row in Table 2.2.

E. The prevalence of a disease or risk factor can be quantified best with cross-sectional survey. See "cross-sectional survey" row in Table 2.2.

F. The only feasible study design for the study of very rare disorders is a case–control study. See "case–control study" row in Table 2.2.

## FURTHER READING

Centre for Evidence-Based Medicine (CEBM). Study designs. 2014. Available at http://www.cebm.net/study-designs. Accessed July 21, 2015.

## 14. ANSWER: B

In this study, the analysis to be performed is to compare means between two independent groups. Given that the data are normally distributed, one can utilize a parametric test to compare the two groups. The appropriate parametric statistical procedure to compare the means of two independent groups is a Student's *t*-test. In Table 2.3, common analysis types and statistical procedures are categorized with corresponding parametric and nonparametric tests.

*Table 2.2* ATTRIBUTES OF RESEARCH STUDY DESIGNS

| STUDY DESIGN | DESCRIPTION | ADVANTAGES | DISADVANTAGES |
|---|---|---|---|
| Randomized controlled trial(RCT) | An experimental comparison study in which randomization is used to allocate participants into control/placebo or intervention/treatment groups. This is the best design to study the effect of an intervention. | • Unbiased distribution of confounders<br>• Blinding<br>• Statistical analysis facilitated by randomization | • Time-consuming and costly<br>• Volunteer bias |
| Crossover design | Each study participant has both treatments or interventions. Subjects are randomized to which treatment they receive first. At the crossover point, the subjects switch treatments. | • Subjects serve as their own control, leading to reduced sample size requirements.<br>• All subjects receive the treatment or intervention at some point.<br>• Blinding | • Not a good design for nonreversible outcomes where treatment or intervention leads to a permanent change or cure<br>• Not good for treatments with lengthy or unknown washout period |
| Cohort study | Subjects are identified who have already been exposed, or not exposed, to the factor. Data are then collected. The design is best for determining the effect of predictive risk factors on an outcome. | • Timing and directionality of events can be established.<br>• It is more convenient and less expensive than an RCT. | • Difficult to identify controls and blind<br>• Possibility of hidden confounder<br>• No randomization<br>• Not suited for rare diseases |
| Case–control study | A careful process is used to identify patients with or without a particular disease or outcome. Data are then collected on exposure to factors of interest. | • Fast and inexpensive<br>• Feasible for rare disorders<br>• Smaller sample size required in comparison to cross-sectional study | • Relies on historical data or recall to determine exposure<br>• Possibility of confounders<br>• Potential recall and selection bias |
| Cross-sectional survey | Exposure and outcome are measured at the same time in a defined population. This is best for determining the prevalence of a disease or risk factor. | • Inexpensive<br>• Simple<br>• No ethical implications | • Established association not causality<br>• Possible recall bias<br>• Neyman bias |

*Table 2.3* PARAMETRIC AND NONPARAMETRIC STATISTICAL PROCEDURES BY TYPE OF ANALYSIS

| ANALYSIS TYPE | EXAMPLE | PARAMETRIC TEST | NONPARAMETRIC TEST |
|---|---|---|---|
| Compare means between two independent groups | Is the mean pain score at baseline for patients assigned to treatment group different from the mean pain score for patients assigned to the placebo group? | Student's *t*-test | Wilcoxon rank-sum test |
| Compare two numerical measurements taken from the same individuals | Was there a significant change in quality of life scores between baseline and the 3-month follow-up measurement in the treatment group? | Paired *t*-test | Wilcoxon signed-rank test |
| Compare means between three or more independent groups | Do baseline physical functioning scores differ at baseline in an experiment with three distinct groups (placebo, drug 1, and drug 2)? | Analysis of variance (ANOVA) | Kruskal–Wallis test |
| Compare multiple numerical measurements taken from the same individuals | Was there a significant change in pain scores in patients receiving treatment measured at baseline, 1 month, 3 months, and 6 months? | Repeated measures ANOVA | Friedman test |

## FURTHER READING


Hoskin T. Parametric and nonparametric: Demystifying the terms. Available at http://www.mayo.edu/mayo-edu-docs/center-for-translational-science-activities-documents/berd-5-6.pdf. Accessed July 23, 2015.

Sheskin DJ. *Handbook of Parametric and Nonparametric Statistical Procedures*. 5th ed. New York, NY: Chapman & Hall/CRC Press; 2011.


## 15. ANSWER: C

Comprehension of the results of an RCT entails that readers must have a complete understanding of its design, conduct, analysis, and interpretation. In order for this to occur, the authors of the study must provide complete transparency of all details. In the mid-1990s, CONSORT was developed by an international group of clinical trialists, statisticians, epidemiologists, and biomedical journal editors as a means of improving reporting of RCTs. The CONSORT Statement, most recently updated in 2010, is an evidence-based minimum set of recommendations including a checklist and flow diagram for reporting RCTs (Figure 2.1). It is meant to facilitate the complete and transparent reporting of trials and aid in their critical appraisal and interpretation.

Although use of the CONSORT Statement is not universal and not required by all medical journals and texts, a Cochrane review by Turner et al. concluded that journal endorsement of the CONSORT Statement may beneficially influence the comprehensiveness of RCT and trial reporting published in medical journals and texts.

## FURTHER READING


Moher D, Schulz KF, Altman D. The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA*. 2001;285(15):1987–1991.

Turner L, Shamseer L, Altman DG, et al. Consolidated Standards of Reporting Trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *Cochrane Database Syst Rev*. 2012; Issue 11:1–162.


## 16. ANSWER: B

In determining clinically important changes for outcome measures in the study of pain, interpretation of two separate aspects of the results must be distinguished. First, it must be established what change in the outcome measure represents a clinically meaningful difference for patients. Second, it must be established what difference in the magnitude of the response between the control and treatment groups is deemed to be large enough to ascertain the therapeutic significance of the results.

For clinical trials designed to evaluate the efficacy of chronic pain therapies, the primary outcome of interest commonly involves reduction in pain score intensity. Multiple studies have been performed to evaluate the magnitude of pain reduction that represents a clinically meaningful response to the pain treatment for patients, and an IMMPACT publication summarized the results with recommendations as noted in Box 2.3.

*Box 2.3* CLINICALLY MEANINGFUL CHANGES IN VISUAL ANALOGUE SCALE PAIN SCORES

- Minimal clinically meaningful change
  - Raw pain score change of approximately 1 point
  - 10–20% reduction in chronic pain intensity
- Moderate clinically meaningful change
  - Raw pain score change of approximately 2 points
  - ≥30% reduction in chronic pain intensity
- Substantial clinically meaningful change
  - Raw pain score change of approximately 4 points
  - ≥50% reduction in chronic pain intensity

CONSORT
TRANSPARENT REPORTING of TRIALS

**CONSORT 2010 Flow Diagram**

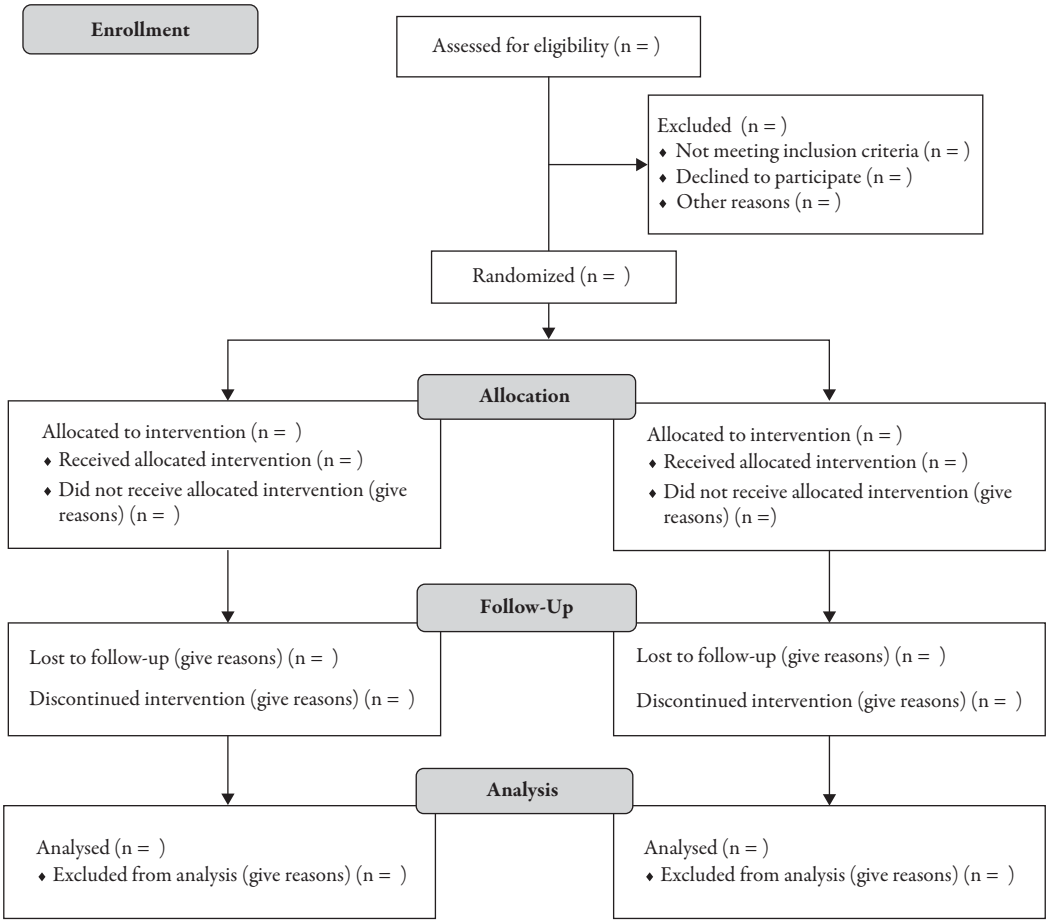


Figure 2.1 The CONSORT flow diagram.
SOURCE: CONSORT Group (http://www.consort-statement.org/consort-statement/flow-diagram).

## FURTHER READING


Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9(2): 105–121.

Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical Importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149–158.

Hanley MA, Jensen MP, Ehde DM, et al. Clinically significant changes in pain intensity ratings in persons with spinal cord injury or amputation. *Clin J Pain*. 2006;22:25–31.

Salaffi F, Stancati A, Silvestri CA, et al. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *Eur J Pain*. 2004;8: 283–291.


## 17. ANSWER: A

The matter of which participants are to be included in a study's data analysis often arises during clinical research trials. Even the most carefully managed and well-designed trial cannot be perfectly executed. The protocol may not be exactly adhered to, outcome and response variable data may be missing, and some patients may not actually have been eligible for the study based on inclusion and exclusion criteria issues. This can lead to controversy when planning the statistical analyses for the data because these problems can introduce bias and potentially disrupt the validity of the results.

The intention-to-treat principle states that all participants randomized and all events should be accounted for in

the primary analysis based on the group to which participants were randomized, regardless of whether or not they adhered to the assigned intervention. Following the intention-to-treat principle may underestimate the full effect of the treatment, but it guards against the more pressing issue of biased results. A per protocol analysis only includes participants who were fully adherent to the protocol with regard to the assigned study medication, follow-up visits and/or measurements, and had no other protocol violations. The main issue with per protocol analysis is that participants who adhere to study treatment and protocol may be different than those who drop out in ways that are related to the outcome of interest. If the results of intention-to-treat and per protocol analyses are different, then the intention-to-treat analysis results typically predominate for estimates of efficacy because they maintain the value of randomization. Unlike per protocol analysis, intention-to-treat analyses can only bias the estimated effect in the conservative direction by favoring the null hypothesis.

## FURTHER READING


Friedman LM, Furberg CD, DeMets DL. Issues in data analysis. In: *Fundamentals of Clinical Trials*. 4th ed. New York, NY: Springer; 2010:345–390.

Grady D, Cummings SR, Hulley SB. Alternative trial designs and implementation issues. In: Hully SB, Cummings SR, Browner SR, et al. (Eds.), *Designing Clinical Research*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:163–182.

Piantadosi S. Counting subjects and events. In: *Clinical Trials: A Methodologic Perspective*. 2nd Ed. Hoboken, NJ: Wiley; 2005:395–407.


## 18. ANSWER: C

Variables can be divided broadly into numerical and categorical categories with further subclassifications as outlined in Table 2.4.

*Table 2.4* CLASSIFICATION OF VARIABLES

| CLASS | SUBCLASS | DEFINITION |
|---|---|---|
| Categorical | Nominal | Variables that have two or more categories but lack any intrinsic order<br>Example: Male or female |
| | Ordinal | Variables that have two or more categories that can be ordered or ranked<br>Example: Strongly agree, moderately agree, etc. |
| Numerical | Interval | Numerical values that can be measured along a continuum<br>Example: Temperature |
| | Ratio | Numerical values measured along a continuum where zero of that variable indicates that none of that variable is present<br>Example: Weight |

## FURTHER READING


Laerd Statistics. Understanding the different types of variable in statistics. 2015. Available at https://statistics.laerd.com/statistical-guides/types-of-variable.php. Accessed July 27, 2015.


## 19. ANSWER: C

In a double-blinded study, both patients and providers are unaware of the patients' group assignment. In a triple-blinded study, another group, such as support staff or data analyzers, is also blinded. Randomization is a process of selecting from a group in a manner that makes equal distribution of confounders likely. Randomization will not work as well with small groups. Stratification is a strategy in which patients are intentionally divided by an important characteristic prior to randomization. Confounding occurs when study results are influenced by a factor other than that which is being studied. When a sample is skewed, it may be due to sampling error or related bias. For example, if diabetic patients are more likely than nondiabetics to volunteer for a study, that is a form of volunteer bias.

## FURTHER READING


Stomp on Step 1. Confounding, randomization & blinding. 2015. Available at http://www.stomponstep1.com/confounding-placebo-stratification-randomization-blinding. Accessed July 27, 2015.


## 20. ANSWER: E

Four situations are possible when performing statistical tests to try to reject the null hypothesis in favor of the alternative hypothesis when interpreting the results of a study. In two of these situations, assuming the study is free from bias, the findings in the sample and what is reality in the population are concordant, and the inference by the investigator(s) will be correct. However, in the other two instances, a type I or type II error has been made, and the inference will not be correct.

Prior to beginning the study, the investigator(s) determines a priori what are the maximum chances he or she will accept in making type I or type II errors. The probability of committing a type I error is also known as $\alpha$ or the significance level. A type I error occurs when the null hypothesis is rejected when in reality there actually is no association between the predictor and outcome variable (a false-positive finding). The probability of a type II error is known as $\beta$. A type II error occurs when there is a failure to reject the null hypothesis when in reality an association does exist between predictor and outcome (a false-negative finding). Power is specified as $1 - \beta$ and is the probability of correctly rejecting

the null hypothesis in the study sample if the actual effect in the population is greater than or equal to the effect size.

In an ideal world, both $\alpha$ and $\beta$ would be set at zero, thus eliminating the possibility of false-positive or false-negative results. In real-life practice, these values are made as small as possible, with the caveat that the sample size will need to increase as these values decrease.

## FURTHER READING


Browner WS, Newman TB, Hulley SB. Getting ready to estimate sample size: Hypotheses and underlying principles. In: Hully SB, Cummings SR, Browner SR, et al. (Eds.), *Designing Clinical Research*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:51–63.

Friedman LM, Furberg CD, DeMets DL. Sample size. In: *Fundamentals of Clinical Trials*. 4th ed. New York, NY: Springer; 2010:133–167.


## 21. ANSWER: A

The crossover design is a special type of RCT in which each study treatment is administered at different times to every subject enrolled in the study. Participants in this type of design "cross over" or "switch" from one treatment to another by this strategy, with the intent to estimate differences between them. Typically, half of the participants are randomly assigned to start with one treatment (or control) and then switch to the other treatment (or control). In the case presented in this question, half would start with drug A and switch to drug B, and the other half would start with drug B and switch to drug A (Figure 2.2). This is the simplest type of crossover trial and is called the two-treatment, two-period design. More complex crossover trial designs may be employed in various clinical circumstances.

The crossover design has multiple advantages for researchers. One advantage is that it minimizes variability because each participant serves as his or her own control and the subsequent paired analyses substantially increase the statistical power of the trial in that fewer participants are required. Thus, the crossover design takes advantage of making treatment comparisons based on within- rather than between-subject differences. This allows the treatment difference to be estimated with greater precision and less possibility for confounding. Recruitment may also be easier with this type of design because all subjects will receive all treatments under investigation, which may be an attractive attribute for some patients who are concerned about participating in clinical trials in which they may be randomized to a no-treatment or placebo arm.

Disadvantages of the crossover design are related to the issue of carryover effects and dropouts. Carryover effects are the residual influence of the intervention on the outcome during the period after which it has been discontinued. To reduce carryover effect, the investigator can use an untreated "washout" period between treatments with the hope that the outcome variable will return to its baseline before starting the next intervention. Another concern for carryover effects is if they lead to a permanent change or cure in the underlying condition of the patient. In this instance, the treatment during the second period could appear falsely or artificially superior. Finally, the patients' condition could change in the second treatment phase of the study, which possibly may affect how they respond to the second treatment.

The issue of dropouts is of concern for two reasons. First, the participant is exposed to more drugs or treatments

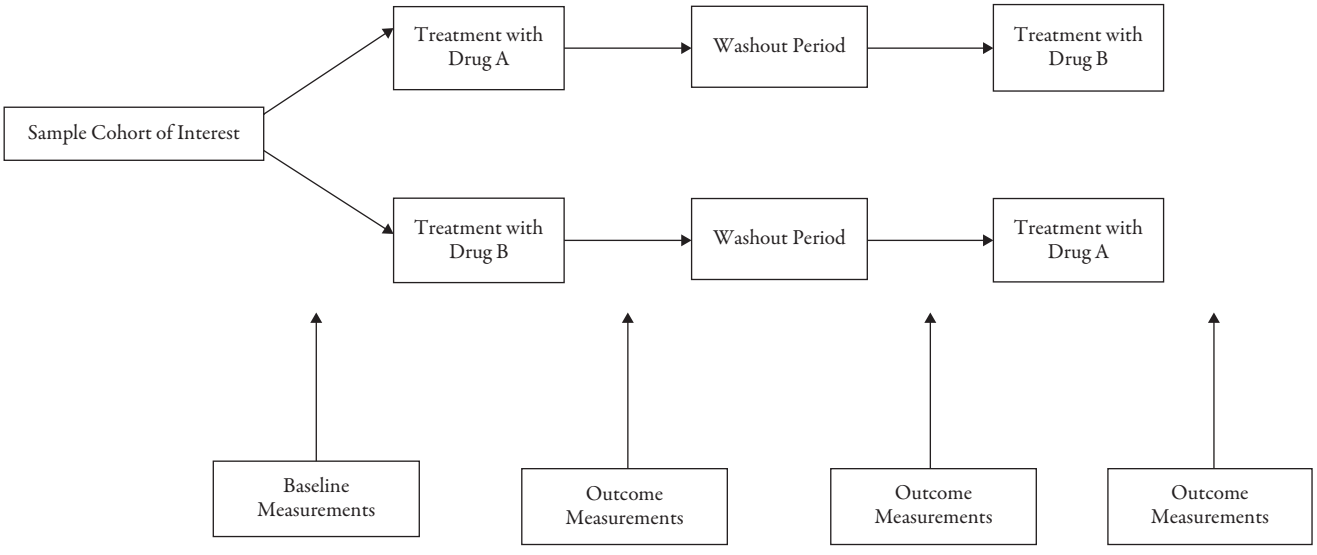


Figure 2.2 Schematic of a two-treatment, two-period, crossover randomized trial design.

in a crossover trial, increasing the chance of side effects that could contribute to dropping out. Second, the study is usually longer than a regular RCT, thus providing a longer period of opportunity to drop out. The consequences of dropouts are more impactful in a crossover design because the data loss is more significant; for example, if a participant drops out in the second treatment phase, the participant's data cannot be analyzed using only the first phase because that participant was acting as his or her own control and determining a treatment effect cannot occur.

## FURTHER READING


Friedman LM, Furberg CD, DeMets DL. Basic study design. In: *Fundamentals of Clinical Trials*. 4th ed. New York, NY: Springer; 2010:67–96.

Grady D, Cummings SR, Hulley SB. Alternative trial designs and implementation issues. In: Hully SB, Cummings SR, Browner SR, et al. (Eds.), *Designing Clinical Research*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:163–182.

Piantadosi S. Crossover designs. In: *Clinical Trials: A Methodologic Perspective*. 2nd ed. Hoboken, NJ: Wiley; 2005:515–527.


## 22. ANSWER: C

Certain groups of participants are considered to be particularly vulnerable to undue influence or coercion in a research setting. These groups, as outlined in 45 CFR 46, are children, wards of the state, prisoners, pregnant women and fetuses, persons who are mentally disabled or otherwise cognitively impaired, and economically or educationally disadvantaged persons. IRBs that review research studies involving all categories of vulnerable patients must determine that their use is adequately justified and that additional safeguards are implemented to minimize risks unique to each group.

## FURTHER READING


US Department of Health & Human Services. CFR—Code of Federal Regulations Title 45, Part 46. Available at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html. Accessed July 27, 2015.

US Department of Health and Human Services. IRB Guidebook: Chapter VI Special Classes of Subjects. Available at http://archive.hhs.gov/ohrp/irb/irb_chapter6.htm. Accessed July 27, 2015.


## 23. ANSWER: E

There are several variations on how sample sizes are estimated for a study or experiment, but there are common features and steps, including the following: stating the null hypothesis and either a one- or two-sided alternative hypothesis, the appropriate statistical test based on type of predictor and outcome variable in the hypotheses, a reasonable effect size between the two study groups, variability, and an a priori determination of $\alpha$ and $\beta$. Even if the exact value for one or more of these steps is uncertain or unknown, it is important to estimate the sample size prior to starting the study and early in the design phase. Many clinical trials are performed that lack the statistical power or ability to detect treatment effects of a magnitude that has some clinical importance. Conversely, some sample size estimations may assume an unrealistically large intervention effect, meaning the power for more realistic and smaller effects will be low. Finally, the danger in studies with low statistical power is that treatments that could be beneficial are discarded due to not finding statistical significance and may never be investigated again. Due to the approximate nature of sample size calculations, investigators should try to balance being realistic with being conservative in estimating the parameters discussed here.

## FURTHER READING


Browner WS, Newman TB, Hulley SB. Estimating sample size and power: Applications and examples. In: Hully SB, Cummings SR, Browner SR, et al. (Eds.), *Designing Clinical Research*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:65–94.

Friedman LM, Furberg CD, DeMets DL. Sample size. In: *Fundamentals of Clinical Trials*. 4th ed. New York, NY: Springer; 2010:133–167.


## 24. ANSWER: B

In designing a research study, one of the most important components is creating selection criteria that define the population to be studied. This is because of the possible effects of prognostic and selection factors on differences in outcome. The inclusion criteria define the main characteristics of the target population that pertain to the research question. Inclusion criteria typically include demographic characteristics (age, gender, and ethnicity), clinical characteristics (the disease being studied and its severity), geographic characteristics (patients from investigator's clinic or hospital or patients outside the investigator's practice), and time characteristics (study time frame from start to finish). Ultimately, inclusion criteria should be as specific as possible, sensible, used consistently throughout the study, and provide the basis for understanding to whom the published results and conclusions apply.

Exclusion criteria, on the other hand, indicate the subsets and characteristics of the population that might interfere with follow-up efforts, the quality of the data, or

high risk of possible side effects. In clinical trials, exclusions tend to include specific causes of concern for the safety of the participants. As a good overall rule, having as few exclusion criteria as possible helps keep recruitment simple and preserves the number of potential study subjects.

### FURTHER READING


Hulley SB, Newman TB, Cummings SR. Choosing the study subjects: Specification, sampling, and recruitment. In: Hully SB, Cummings SR, Browner SR, et al. (Eds.), *Designing Clinical Research*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:27–36.

Piantadosi S. The study cohort. In: *Clinical Trials: A Methodologic Perspective*. 2nd ed. Hoboken, NJ: Wiley; 2005:309–330.


## 25. ANSWERS:

A. The inverse of ARR is equal to NNT). NNT represents how many people need to be treated or exposed to an intervention in order for one person to have an improved outcome. To calculate NNT, ARR must first be determined. ARR is defined as the difference between the control event rate and the experimental event rate. NNT is equal to the inverse of ARR.

### FURTHER READING


Centre for Evidence-Based Medicine. Number needed to treat (NNT). 2014. Available at http://www.cebm.net/number-needed-to-treat-nnt. Accessed July 26, 2015.


B. Specificity correlates to the proportion of negatives that are correctly identified as such. Sensitivity is a measure of how likely a test will correctly identify a condition when it is present. Sensitivity is calculated as the number of true positives divided by the sum of true positives and false negatives. Specificity, on the other hand, is a measure of the likelihood that a person without a disease will have a negative test. It is calculated as the number of true negatives divided by the sum of the true negatives and false positives.

### FURTHER READING


Williams M. Sensitivity and specificity: Precision of the clinical exam. 2015. Available at https://www.med.emory.edu/EMAC/curriculum/diagnosis/sensand.htm. Accessed July 26, 2015.


C. Positive predictive value is calculated as the number of true positives divided by the sum of true positives and false positives. It is the probability that a patient with a positive test actually has the disease. Negative predictive value, on the other hand, is the number of true negatives divided by the sum of the true negatives and false negatives.

### FURTHER READING


Williams M. Sensitivity and specificity: Precision of the clinical exam. 2015. Available at https://www.med.emory.edu/EMAC/curriculum/diagnosis/sensand.htm. Accessed July 26, 2015.


D. Power quantifies the likelihood of identifying a significant effect when it exists. It can be calculated as $1 - \beta$.

### FURTHER READING


Calkins K. Power and sample size: Applied statistics. 2015. Available at http://www.andrews.edu/~calkins/math/edrm611/edrm11.htm. Accessed July 26, 2015.

# 3.

# PAIN RESEARCH

## PLACEBO, ANIMAL MODELS, ETHICS, AND EPIDEMIOLOGY

*David A. Edwards*

## INTRODUCTION

Research of pain requires not only that basic ethical standards for human studies research be followed but also that special consideration be given due to the potential for human suffering. The use of placebos as controls became widespread after World War II with the adoption of the randomized controlled trial. Other study designs have elucidated the risk factors for pain. The prevalence of pain in society is a measure of the burden of pain.

Experimentation using animals in pain research has provided considerable insight into the pathophysiology of pain in humans. Because the experience of pain is subjective, the study of pain in animals must be done in a way that limits potential suffering. Nociception and the response in animals must be considered to reflect pain, and so ethical principles to limit potential suffering in animals guide research in this area.

Historical abuses in human experimentation have driven the development of ethical guidelines for human subjects research. The *Belmont Report* serves as the modern standard of basic ethical principles on which institutional review boards (IRBs) judge human research studies.

## QUESTIONS

**1. In randomized controlled trials (RCTs), placebo response size is often difficult to quantify. Which of the following is not a confounder of positive placebo response in RCTs?**

A. Response bias
B. Regression to the mean
C. Natural course of disease
D. An educated patient
E. Fluctuation in symptoms

**2. A 50-year-old female is asked to rate her pain after receiving a placebo pill. She notices the research observer watching her and smiling; thus, she reports an improvement in her pain. This phenomenon is known as?**

A. Response bias
B. Regression to the mean
C. Hawthorne effect
D. Mesmerism
E. Placebo response

**3. Which of the following is true about the placebo effect?**

A. It is a psychobiological event that can be attributed to the entire treatment experience.
B. Patient expectations negatively impact placebo response size.
C. Classical conditioning is the primary reason for the placebo response.
D. The Yale–Brown Compulsive Scale is used to rule out poor candidates in placebo-controlled trials.

**4. Which of the following is a true definition of nocebo?**

A. The paucity of effect from placebo
B. Negative side effects of a placebo
C. An active treatment not meant to cause the effect observed
D. A nonmedication placebo treatment
E. The observed effect of a placebo

**5. A practitioner injects lidocaine into muscle trigger points and describes to the patient the triggering**