KNOW PAIN IN GENERAL
# Development Committee

<table>
<thead>
<tr>
<th>Name</th>
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<th>City, Country</th>
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<tbody>
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<td>Beijing, China</td>
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<td>Ankara, Turkey</td>
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*This program was sponsored by Pfizer Inc.*
Learning Objectives

• After completing this module, participants will be able to:
  – Describe the classification of pain according to pain mechanisms, duration, severity and type of tissue involved
  – Discuss overall prevalence of pain
  – Assess patients presenting with pain
  – Select appropriate pharmacological and non-pharmacological strategies based on type of pain
  – Know when to refer patients to specialists
Table of Contents

• What is pain?
• How common is pain?
• What are the underlying types of pain?
• How should pain be assessed in clinical practice?
• How should pain be treated based on its pathophysiology?
What is pain?

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

International Association for the Study of Pain (IASP) 2011
Pain Is the 5th Vital Sign

Overview of Pain

Protective role: vital early warning system
- Senses noxious stimuli
- Triggers withdrawal reflex and heightens sensitivity after tissue damage to reduce risk of further damage

Unpleasant experience:
- Suffering – physical, emotional and cognitive dimensions
- Continuous unrelieved pain can affect physical (e.g., cardiovascular, renal, gastrointestinal systems, etc.) and psychological states

Maladaptive response:
- Neuropathic and central sensitization/dysfunctional pain
- Not protective
- Lessens quality of life

Discussion Question

DOES EVERYONE FEEL PAIN THE SAME WAY?
FROM A PRACTICAL POINT OF VIEW, HOW DO YOU CLASSIFY PAIN?
Pain Classification


Duration
- Acute
- Chronic

Location
- Head
- Low back
- Etc.

Severity
- Mild
- Moderate
- Severe

Pathophysiology
- Nociceptive
- Neuropathic
- Central sensitization/dysfunctional
The Pain Continuum

Time to resolution

Acute pain

Insult

Normal, time-limited response to ‘noxious’ experience (less than 3 months)

- Usually obvious tissue damage
- Serves a protective function
- Pain resolves upon healing

Chronic pain

Pain that has persisted beyond normal tissue healing time (usually more than 3 months)

- Usually has no protective function
- Degrades health and function

Acute pain may become chronic

Discussion Question

HOW MANY PATIENTS IN ACUTE PAIN DO YOU SEE DURING A TYPICAL WEEK?
Prevalence of Acute Pain

• **Lifetime** prevalence in general population:
  – Approaches **100%** for acute pain leading to use of analgesics\(^1\)

• **Emergency room** patients:
  – Pain accounts for **>2/3** of emergency room visits\(^2\)

• **Hospitalized** patients:
  – **>50%** report pain\(^3\)

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Discussion Question

WHAT PROPORTION OF PATIENTS IN YOUR PRACTICE SUFFERS FROM CHRONIC PAIN?
Prevalence of Chronic Pain

<table>
<thead>
<tr>
<th>Category</th>
<th>Both genders</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>All countries</td>
<td>38.4</td>
<td>44.9</td>
<td>31.4</td>
</tr>
<tr>
<td>Developing countries</td>
<td>41.1</td>
<td>48.5</td>
<td>31.4</td>
</tr>
<tr>
<td>Developed countries</td>
<td>37.3</td>
<td>43.1</td>
<td>31.0</td>
</tr>
</tbody>
</table>

Multiple pain mechanisms may coexist (mixed pain)

Nociceptive pain
- Somatic
- Visceral

Neuropathic pain
- Peripheral
- Central

Central sensitization/dysfunctional pain

What is nociceptive pain?

**Definition**

- Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors
- Can be somatic or visceral

**Pain Quality**

- Usually aching or throbbing
- Usually time-limited (resolves when damaged tissue heals)
- Usually well localized if somatic
- May be referred if visceral
- Can become chronic

Nociceptive Pain

Somatic
- Musculoskeletal injury
- Trauma
- Post-operative pain
- Burn pain

Visceral
- Ischemic, e.g., myocardial infarction
- Abdominal colic
- Infection, e.g., pharyngitis
- Dysmenorrhea
# Somatic vs. Visceral Pain

<table>
<thead>
<tr>
<th>Somatic</th>
<th>Visceral</th>
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</thead>
<tbody>
<tr>
<td>• Nociceptors are involved</td>
<td>• Involves hollow organ and smooth muscle nociceptors that are sensitive to stretching, hypoxia and inflammation</td>
</tr>
<tr>
<td>• Often well localized</td>
<td>• Pain is usually referred, poorly localized, vague and diffuse</td>
</tr>
<tr>
<td>• Usually described as throbbing or aching</td>
<td>• May be associated with autonomic symptoms (e.g., pallor, sweating, nausea, blood pressure and heart rate changes)</td>
</tr>
<tr>
<td>• Can be superficial (skin, muscle) or deep (joints, tendons, bones)</td>
<td></td>
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</tbody>
</table>
Referred Pain

Nociception: Neural Process of Encoding Noxious Stimuli

Consequences of encoding may be autonomic (e.g., elevated blood pressure) or behavioral (motor withdrawal reflex or more complex nocifensive behavior). Pain perception is not necessarily implied.

Transduction via Endogenous Mediators

Noxious stimuli
- Mechanical
- Thermal
- Chemical

Mediators
- Prostaglandins
- Leukotrienes
- Substance P
- Histamine
- Bradykinin
- Serotonin
- Hydroxyacids
- Reactive oxygen species
- Inflammatory cytokines and chemokines

Receptors/channels on nociceptors

Transmission via Neurotransmitters

1. Impulses reach terminals of presynaptic neuron
2. Glutamate is released into synaptic cleft
3. Glutamate binds to AMPA receptor
4. Impulse is transmitted to postsynaptic neuron

AMPA = 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid; NK = neurokinin; NMDA = N-methyl-D-aspartate

Pain Modulation

- Pain is modulated via **ascending nociceptive** and **descending inhibitory/facilitatory** spinal tracts.

<table>
<thead>
<tr>
<th>Ascending Nociceptive</th>
<th>Descending Inhibitory/facilitatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>C fibers</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Aδ fibers</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
</tr>
</tbody>
</table>

References:
- Benarroch EE. *Neurology* 2008; 71(3):217-21;
Pain Perception

• Spinal cord transmits pain signals to specific nuclei in the thalamus, and from there to wide variety of regions in the brain – collectively known as the “pain matrix”

• Pain perception can also be altered without any external stimuli (i.e., through emotion, distraction, placebo, etc.)

Inflammation

Damaged tissue
Inflammatory cells
Tumor cells

Inflammatory chemical mediators

Prostanoids
Cytokines
Growth factors
Kennis
Purines
Amines
Ions

Changed responsiveness of nociceptors (peripheral sensitization)

Changed responsiveness of neurons in CNS (central sensitization)

Nociceptive afferent fiber

Spinal cord

Brain

CNS = central nervous system
Recognizing Neuropathic Pain

Common descriptors
- Shooting
- Electric shock-like
- Burning
- Tingling
- Numbness

Post-stroke pain
Diabetic peripheral neuropathy
Lumbar radicular pain
Postherpetic neuralgia
Chronic post-surgical pain

What is neuropathic pain?

<table>
<thead>
<tr>
<th>Definition</th>
<th>Pain Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pain caused by a lesion or disease of the somatosensory nervous system</td>
<td>• Burning</td>
</tr>
<tr>
<td>• Can be peripheral or central</td>
<td>• Lancinating</td>
</tr>
<tr>
<td></td>
<td>• Electric shock-like</td>
</tr>
<tr>
<td></td>
<td>• Often diffuse</td>
</tr>
<tr>
<td></td>
<td>• Frequently with allodynia and/or</td>
</tr>
<tr>
<td></td>
<td>hyperalgesia</td>
</tr>
</tbody>
</table>

Common Descriptors of Neuropathic Pain

- Burning
- Tingling
- Pins and needles
- Electric shock-like
- Numbness

Neuropathic Pain Is Characterized by Changes in Pain Response to Painful Stimuli

Pain intensity

10
9
8
7
6
5
4
3
2
1
0

Stimulus intensity

Hyperalgesia
(increased response to a stimulus that is normally painful)

Allodynia
(pain due to stimulus that does not normally provoke pain)

Response after injury

Normal pain response

Mechanisms of Neuropathic Pain

- Nerve lesion/disease
- Spinal cord Nociceptive afferent fiber
- Loss of inhibitory control
- Central sensitization
- Ectopic discharge
- Peripheral sensitization
- Descending modulation
- Nerve lesion/disease
- Nociceptive afferent fiber
- Spinal cord

References:
What is central sensitization/dysfunctional pain?

<table>
<thead>
<tr>
<th>Definition</th>
<th>Examples</th>
<th>Pain Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Amplification of neural signaling within the CNS that elicits pain</td>
<td>• Fibromyalgia</td>
<td>• Burning</td>
</tr>
<tr>
<td>hypersensitivity</td>
<td>• Irritable bowel syndrome</td>
<td>• Lancinating</td>
</tr>
<tr>
<td></td>
<td>• Interstitial cystitis</td>
<td>• Electric shock-like</td>
</tr>
<tr>
<td></td>
<td>• Temporomandibular joint pain</td>
<td>• Often diffuse</td>
</tr>
<tr>
<td></td>
<td>• May be present in many patients with chronic low back pain, osteoarthri</td>
<td>• Frequently with</td>
</tr>
<tr>
<td></td>
<td>tis and rheumatoid arthritis</td>
<td>alldynia and/or hyperalgesia</td>
</tr>
</tbody>
</table>

CNS = central nervous system
Importance of Pain Assessment

Pain is a significant predictor of morbidity and mortality.

- Screen for red flags requiring immediate investigation and/or referral
- Identify underlying cause
  - Pain is better managed if the underlying causes are determined and addressed
- Recognize type of pain to help guide selection of appropriate therapies for treatment of pain
- Determine baseline pain intensity to future enable assessment of efficacy of treatment

Discussion Question

HOW DO YOU ASSESS PAIN IN YOUR PRACTICE?
Pain History Worksheet

- Site of pain
- What causes or worsens the pain?
- Intensity and character of pain
- Associated symptoms?
- Pain-related impairment in functioning?
- Relevant medical history

Locate the Pain

Body maps are useful for the precise location of pain symptoms and sensory signs.*

*In cases of referred pain, the location of the pain and of the injury or nerve lesion/dysfunction may not be correlated
Determine Pain Intensity

Simple Descriptive Pain Intensity Scale

0–10 Numeric Pain Intensity Scale

Faces Pain Scale – Revised

Discussion Question

DO YOU USE A SCREENING TOOL FOR NEUROPATHIC PAIN IN YOUR PRACTICE? IF SO, WHICH TOOL AND WHY?
## Neuropathic Pain Screening Tools

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>LANSS</th>
<th>DN4</th>
<th>NPQ</th>
<th>painDETECT</th>
<th>ID Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pricking, tingling, pins and needles</td>
<td>X</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Electric shocks of shooting</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot or burning</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbness</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Pain evoked by light touching</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Painful cold or freezing</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical examination**

- Brush allodynia: X
- Raised soft touch threshold: X
- Altered pin prick threshold: X

Neuropathic pain screening tools rely largely on common verbal descriptors of pain. Select tool(s) based on ease of use and validation in the local language. Some screening tools also include bedside neurological examination.

DN4 = Douleur Neuropathique en 4 Questions (DN4) questionnaire; LANSS = Leeds Assessment of Neuropathic Symptoms and Signs; NPQ = Neuropathic Pain Questionnaire

Evaluate Impact of Pain on Functioning

Anxiety and depression

Sleep disturbances

Whenever possible, it is important to identify and treat the underlying cause of pain!
Be Alert for Red Flags

Evaluate for patients presenting with pain the presence of red flags!

Initiate appropriate investigations/management or refer to specialist

Deciding on the Best Course of Treatment for the Patient

Collaborative Care

- Patient as the ultimate manager of his/her illness
- Family
- General practitioner ± other health care professional(s)

Goals in Pain Management

• Involve the patient in the decision-making process
• Agree on realistic treatment goals **before** starting a treatment plan
Multimodal Treatment of Pain Based on Biopsychosocial Approach

- Pharmacotherapy
- Stress management
- Interventional pain management
- Biofeedback
- Complementary therapies
- Education
- Physical therapy
- Occupational therapy
- Sleep hygiene
- Lifestyle management

References:
WHAT NON-PHARMACOLOGICAL APPROACHES TO MANAGING PAIN DO YOU INCORPORATE INTO YOUR PRACTICE? ARE THERE NON-PHARMACOLOGICAL MODALITIES YOUR PATIENTS REGULARLY ASK ABOUT?
Non-pharmacological Interventions

- Non-pharmacological interventions are commonly used in clinical practice
- Establishing reliable evidence of efficacy and effectiveness can be challenging in terms of design and interpretation of studies

<table>
<thead>
<tr>
<th>Type of therapy</th>
<th>Examples</th>
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</thead>
<tbody>
<tr>
<td>Psychological</td>
<td>• Hypnosis</td>
</tr>
<tr>
<td></td>
<td>• Relaxation</td>
</tr>
<tr>
<td></td>
<td>• Cognitive behavioral therapy</td>
</tr>
<tr>
<td>Physical</td>
<td>• Acupuncture</td>
</tr>
<tr>
<td></td>
<td>• Transcutaneous electrical nerve stimulation</td>
</tr>
<tr>
<td></td>
<td>• Healing touch and massage</td>
</tr>
<tr>
<td></td>
<td>• Occupational therapy</td>
</tr>
<tr>
<td>Clinical process</td>
<td>• Pain assessment</td>
</tr>
<tr>
<td></td>
<td>• Physician advice and communication</td>
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<td></td>
<td>• Education</td>
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</tbody>
</table>
Evidence of Potential Benefits of Complementary and Alternative Medicine

<table>
<thead>
<tr>
<th></th>
<th>Arthritis</th>
<th>Headache</th>
<th>Low back pain</th>
<th>Neck pain</th>
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</thead>
<tbody>
<tr>
<td>Acupuncture</td>
<td>√</td>
<td></td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>Balneotherapy (mineral baths)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feverfew</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamma linoleic acid</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Glucosamine/chondroitin</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Herbal remedies</td>
<td>X</td>
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<td>X</td>
<td></td>
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<tr>
<td>Massage</td>
<td></td>
<td></td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Spinal manipulation</td>
<td></td>
<td></td>
<td>√</td>
<td>X</td>
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<tr>
<td>Progressive relaxation</td>
<td></td>
<td></td>
<td></td>
<td>√</td>
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<tr>
<td>Prolotherapy</td>
<td></td>
<td></td>
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<td>X</td>
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<tr>
<td>Tai chi</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Yoga</td>
<td></td>
<td></td>
<td></td>
<td>√</td>
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√ = promising evidence of potential benefit; X = limited, mixed or no evidence to support use

Mechanism-Based Pharmacological Treatment of Nociceptive/Inflammatory Pain

Noxious stimuli → Transduction → Nociceptive afferent fiber → Transmission → Spinal cord → Peripheral sensitization → Inflammation → nsNSAIDs/coxibs, opioids

Descending modulation

α2δ ligands
Acetaminophen
Antidepressants
nsNSAIDs/coxibs
Opioids

Ascending input

Perception

Brain

Opioids

Coxib = COX-2 inhibitor; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Acetaminophen

• Action at molecular level is unclear
• Potential mechanisms include:
  – Inhibition of COX enzymes (COX-2 and/or COX-3)
  – Interaction with opioid pathway
  – Activation of serotoninergic bulbospinal pathway
  – Involvement of nitric oxide pathway
  – Increase in cannabinoid-vanilloid tone

What are NSAIDs (nsNSAIDs/coxibs)?

**NSAID = Non-Steroidal Anti-Inflammatory Drug**

- Analgesic effect via inhibition of prostaglandin production
- Broad class incorporating many different medications:

<table>
<thead>
<tr>
<th>Examples of nsNSAIDs:</th>
<th>Examples of Coxibs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Diclofenac</td>
<td>– Celecoxib</td>
</tr>
<tr>
<td>– Ibuprofen</td>
<td>– Etoricoxib</td>
</tr>
<tr>
<td>– Naproxen</td>
<td>– Parecoxib</td>
</tr>
</tbody>
</table>

ASA = acetylsalicylic acid; coxib = COX-2-specific inhibitor; nsNSAID = non-specific non-steroidal anti-inflammatory drug

How do nsNSAIDs/coxibs work?

Coxib = COX-2-specific inhibitor; NSAID = non-steroidal anti-inflammatory drug
nsNSAID = non-specific non-steroidal anti-inflammatory drug

How Opioids Affect Pain

Modify perception, modulate transmission and affect transduction by:

• Altering limbic system activity; modify sensory and affective pain aspects
• Activating descending pathways that modulate transmission in spinal cord
• Affecting transduction of pain stimuli to nerve impulses

Discussion Question

BESIDES NOCICEPTION, WHAT ARE SOME OTHER PATHOPHYSIOLOGICAL MECHANISMS OF PAIN?

WHAT PHARMACOLOGICAL AGENTS MIGHT YOU USE TO TREAT PATIENTS SUFFERING FROM THESE TYPES OF PAIN?
Mechanism-Based Pharmacological Treatment of Neuropathic Pain

Medications affecting peripheral sensitization:
- Capsaicin
- Local anesthetics
- TCAs

Medications affecting descending modulation:
- SNRIs
- TCAs
- Tramadol, opioids

Medications affecting central sensitization:
- $\alpha_2\delta$ ligands
- TCAs
- Tramadol, opioids

Nerve lesion/disease

Descending modulation

SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

Role of $\alpha_2\delta$-Linked Calcium Channels in Neuropathic Pain

Increased numbers of calcium channels

Increased calcium influx

Increased neuronal excitability

INCREASED PAIN SENSITIVITY

Binding of $\alpha_2\delta$ ligands to $\alpha_2\delta$ inhibits calcium channel transport

Calcium channels transported to nerve terminals in dorsal horn

Injury stimulates production of calcium channel

Nerve injury

Note: gabapentin and pregabalin are $\alpha_2\delta$ ligands
How Antidepressants Modulate Pain

Inhibiting reuptake of serotonin and norepinephrine enhances descending modulation.
Assessment of Pain Pathophysiology Can Help Guide Appropriate Medication Therapy

Opioids
For management of **moderate** to **severe** pain in appropriate patients

Most opioid treatment guidelines for chronic pain recommend use for patients after inadequate response to non-opioid therapy*

- Acetaminophen
- nsNSAIDs/coxibs

Nociceptive pain

α₂δ ligands
Antidepressants

- Neuropathic and central sensitization/dysfunctional pain

Mild       Moderate    Severe

*Selected on the basis of the pathophysiology of patient’s pain, provided there are no contraindications for its use
Coxib = COX-2-specific inhibitor; nsNSAID = non-specific non-steroidal anti-inflammatory drug
Analgesics Affect Different Parts of the Pain Pathway

- **Ascending input**
- **Descending modulation**
- **Dorsal horn**
- **Spinothalamic tract**
- **Peripheral nerve**
- **Peripheral nociceptors**

- **Pain**
- **Trauma**

- **α₂δ ligands**
- **Antidepressants**
- **nsNSAIDs/coxibs**
- **Opioids**

- **Local anesthetics**
- **α₂δ ligands**
- **Antidepressants**
- **nsNSAIDs/coxibs**
- **Opioids**

**Coxib** = COX-2 inhibitor; **nsNSAID** = non-specific non-steroidal anti-inflammatory drug

Non-adherence to chronic pain medication is common...

Overall non-adherence: 36-81%

- Overuse: 3-75%
- Underuse: 2-51%
- Misuse: 13-32%

But rates vary substantially from study to study

Strategies to Improve Adherence

- Simplify regimen
- Impart knowledge
- Modify patient beliefs and human behavior
- Provide communication and trust
- Leave the bias
- Evaluate adherence
Key Messages

• Pain is a common yet complex biopsychosocial phenomenon that affects every aspect of a patient’s life
• Pain can be classified into 3 main types according to pathophysiology (found separately or together/mixed type):
  – Pain due to inflammation or tissue damage (nociceptive pain)
  – Pain due to lesion or disease of somatosensory system (neuropathic pain)
  – Pain due to “central sensitization/dysfunctional pain” (terminology in flux)
• The type of pain pathophysiology can guide us to select rational, mechanism-based treatment options
• Optimal management often requires: identifying the red flags, treating the cause and combining pharmacological, biological, psychological/social and interventional techniques