Basic Principles, and Clinical Issues in Pain Management

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Prescribing Controlled Substances:
Critical Issues and Common Pitfalls

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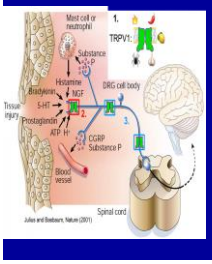
Disclosure/Disclaimer

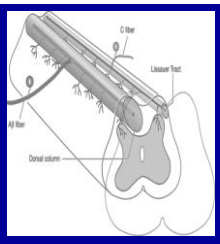
- No conflicts to disclose
- The views and opinions expressed do not necessarily reflect those of the Alabama Board of Medical Examiners (ALBME) or the Medical Association of the State of Alabama (MASA)

Goals

- Describe the neurophysiological processes involved in pain
- Outline the differences between acute and chronic pain
- Review the role of psychosocial factors in chronic pain and opioid effectiveness
- Illustrate clinical conditions, and the associated decision-making process

Peripheral 'Inflammatory Soup'

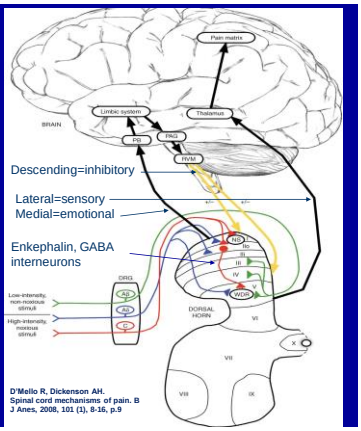




Lissauer's Tract

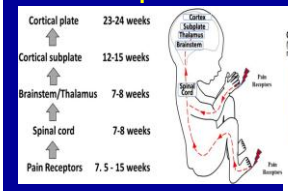
- A- and C-fibers send collaterals along Lissauer's tract.
- Extend up 4-6 segments.
- Activation of primary afferents at L4 may create excitation to L5 and up to T12 with lesser penetration at remote sites.
- Thus, injury at a specific lumbar spinal level can be associated with complaints of pain beyond that particular level.

Pain pathways from periphery to the brain



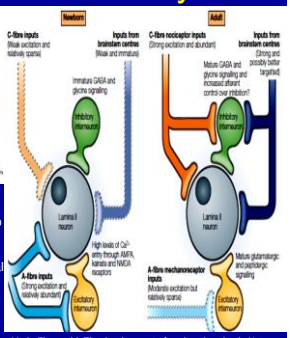
D'Mello R, Dickenson AH. Spinal cord mechanisms of pain. B J Anes, 2008, 101 (1), 8-16, p.9

Development of the 'Pain' System



Development of nociceptive pathways.
7.5-15 weeks: Peripheral pain receptors develop
7-8 weeks: Afferents reach the spinal cord, brainstem, and thalamus
12-15 weeks: Thalamic projections to the cortical subplate emerge
23-24 weeks: Thalamic projections reach the cortical plate.

Thill B. The fetal pain paradox. Front. Pain Res. 2023 4:1128530. doi: 10.3389/fpain.2023.1128



Maria Fitzgerald. The development of nociceptive circuit. Nat Rev Neurosci, 2005, 6, 507-520

Fetal Pain: Existence? Different Type or Kind of Pain?

'Fetal' pain:

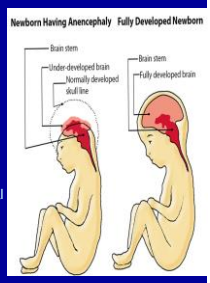
(a) subcortical level: children born with minimal/no, cerebral cortex **(anencephaly)** appear to experience pain

(Grossu, A.O. (2017) What science reveals about fetal pain. Issue Analysis IS15A01 (https://downloads.frc.org/EF/EF15A104.pdf.)

(b) more sensory-related phenomenon; social, emotional, and cognitive factors limited role.

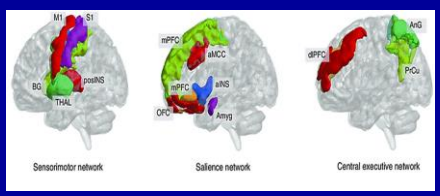
(c) a 'kind' of pain associated with a certain level of developmental maturity vs gestational age. The response of individuals with minimal or no cortical development/function, might be described as 'fetal pain'.

(Doleys, D.M. The emergence of fetal pain: some considerations. *Curr Res Pyshol Behav Sci*. 2023.)



Key Concepts: Resilience vs Dependence

- Resilience: capacity to sustain positive function, and/or to recover quickly, from difficulties
- Salience: quality of being particularly noticeable or important - prominence



Bhatt RR, et al. Chronic pain in children: structural and resting-state functional brain imaging within a developmental perspective. Pediatric Research, 2019

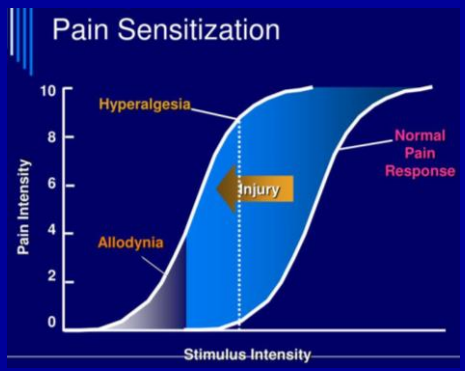
Chronic Pain In US: Incidence (2019-2021)

- CDC
  - > 51 million people (> 20% of US adults) have chronic pain
  - 17 million (~7% of adults) have high-impact chronic pain.
  - More new cases of chronic pain reported than other diabetes, depression, and hypertension

- Rikard SM,et al. Chronic Pain Among Adults — United States, 2019–2021. MMWR Morb Mortal Wkly Rep 2023;72:379–385. DOI: http://dx.doi.org/10.15585/mmwr.mm7215a1
- Nahin RL, et al. Estimated Rates of Incident and Persistent Chronic Pain Among US Adults, 2019-2020. JAMA Network Open. 2023;6(5):e2313563. doi:10.1001/jamanetworkopen.2023.13563 (Reprinted) May 16, 2023

IASP Classification of Pain

Pain-related Terminology

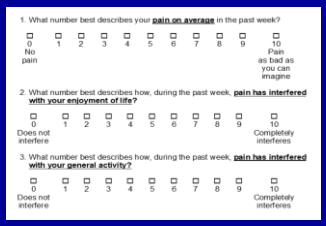


Pain: Assessment

- The verbal expression of pain, is a behavior; considered to be 'part of pain', and not a verbal expression of it. It is not a 1:1 correspondent of the subjective experience of pain
  Wittgenstein L. The Philosophical Review. 1958: 77, 3, pp. 275-320.
  Galafaro F. Pain and forms of life. Philosophical investigations on chronic pain. Esercizi Filosofici 6, 2011; 266-280
- "… the root problem may be neither the high risk or the low efficacy of long term opioid therapy but rather an ***improper focus on reducing pain intensity"*** (p.67) (Sullivan and Ballantyne. Pain, 2016, 157, 65-69)
- The pervasive use of the numerical pain rating (NPR) in the clinical setting ***has been linked to the increase in opioid prescribing*** (Farrar et al, 2001; Sullivan and Ballantyne, 2016).

Alternatives to Assessing Outcomes

- Global Percentage Improvement; 0=100%
- 5-As: Analgesia, adverse events, aberrant drug behavior, affect, activity
- Pain Enjoyment of Life and General Activity (PEG) scale



1. What number best describes your **pain on average** in the past week?

☐ 0 No pain ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Pain as bad as you can imagine

2. What number best describes how, during the past week, **pain has interfered with your enjoyment of life?**

☐ 0 Does not interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely interferes

3. What number best describes how, during the past week, **pain has interfered with your general activity?**

☐ 0 Does not interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely interferes

Younger et al .Curr Pain Headache Rep. 2009; 13(1): 39–4

Pain vs Pathology vs Function

R.A. DOB 5/69
SP lumbar surgery x 8
Work: FT hardware store x 20 years
Meds: GABA 600 bid
hydrocodone 10 qid
NPR: moderate range

'Pain' as a Disease: ***Summary*** of Changes

Physiological Pathology:
- PNS: antidromic activity, peripheral sensitization
- CNS: central sensitization, altered cortical activity

Chemical Pathology: neurotransmitters, inflammatory substances, brain chemistry

Morphological Changes: cell death, sprouting, cortical reorganization

Impact: individual, family, society

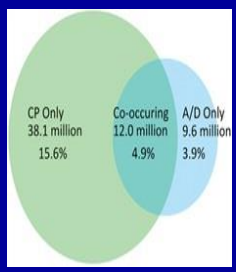
CP is not CP is not CP

- High vs low impact.
- Neuropathic vs Musculoskeletal
- Palliative vs Rehab/functional
- High vs low psych comorbidities
- Polymorphisms

CRPS

Co-existing Chronic Pain and Anxiety/Depression: U.S. Adults: 2019 survey

- ~ 12 million (4.9% of population), co-existing chronic pain and A/D symptoms.
- Unremitted A/D symptoms co-exist in 23.9% of chronic pain vs 4.9% without chronic pain.
- Chronic pain co-exists in 55.6% of adults with unremitted A/D symptoms vs 17% without A/D symptoms.
- Co-existing symptoms associated with limitations in work, house-hold chores, and social activities.
- There is a need to target improving functional outcomes



De La Rose J, wt al Co-occurrence of chronic pain and anxiety/depression symptoms in U.S. adults: prevalence, functional impacts, and opportunities. PAIN, September 21, 2023. | DOI: 10.1097/j.pain.

Psychological/Cognitive Factors Affecting Pain Perception and Behavior

- Pain appraisal: The "meaning" attached to the pain, i.e. expected, accepted, punishment, badge of courage, disease conviction etc
- Beliefs about pain: Patient beliefs regarding the effect of pain on disability, function, emotions, need for medication, assistance for others, control over it
- Coping: Behavioral/cognitive responses to pain e.g. ignore, pray, relax, keep going, distract
- Self-efficacy: Patient beliefs that they and/or the strategies they apply will be effective

Depression

- **S** - Sleep
- **I** - Interest
- **G** - Guilt
- **E** - Energy
- **C** - Concentration
- **A** - Appetite
- **P** - Psychomotor retardation
- **S** - Suicide

Clinical Issues

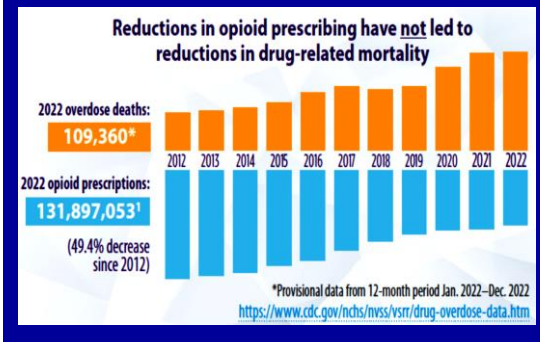
Chronic Pain: Growing Crisis

- Increase incidence
- Decrease availability of medication
- Decrease in prescribers/provides

Availability Affected By

- Production:
  - 68% for oxycodone and 73% for hydrocodone reduction vs 2015
- Distribution
- Dispensing
- Coverage

Overdose Epidemic Report: 2023. AMA



Fentanyl Seizures: 2017- 2024

- US fentanyl seizures increased by > 1700% between 2017 and 2023
- Total seizures: 66,303, 67% in powder form, 33% pills.
- Greatest number in Florida, Arizona, and California
- California: greatest number of pills seized (n = 38.6 million), and greatest weight of powder seized (4315 kg).

JJ Palamar et al. National and regional trends in fentanyl seizures in the United States, 2017–2023 International Journal of Drug Policy. Available online 13 May 2024, 104417

AMA 2023 Recommendations

- Support patients with pain by following CDC's 2022 revised opioid prescribing recommendations and rescinding arbitrary opioid prescribing dose and quantity thresholds, laws and policies. Further support patients with pain be requiring health insurance companies and other payers to make non-opioid pain care alternatives more accessible and affordable, emphasizing social determinants of health, including transportation, housing, employment and other factors.

Overdoes Epidemic Report: 2023. AMA

Prescribing Dilemmas: What to Focus on

- Guidelines: inherently biased, multiple sources (federal, state, local), blatant assertion, lack longevity,
  e.g. DSM 5TR; 60% of panel shared in 14mill dollars-undisclosed industrial funding. 80% of psychiatric meds are prescribed by primary care doctors, -yet not represented proportionately
- Safety: side effects: physical including hormonal; psychosocial (diversion), SUD,
- Effectiveness: Pain, Qol, function, satisfaction
- Evidence-based Medicine: conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. Integrating the **experience** of the clinician, **values** of the patient, and the best available **scientific information.**

Questioning the Right to Pain Relief and its Role in then Opioid Epidemic

- Opioid prescribing: "… the root problem … an improper focus on reducing pain intensity" (p.67) (Sullivan and Ballantyne. Pain, 2016, 157, 65-69)
- AMA, American College of Surgeons, The Joint Commission, AAFP, and CMS have withdrawn their advocacy of the "pain as the 5th vital sign" campaign. (Levy N, Sturgess J, Mills P. "Pain as the fifth vital sign" and dependence on the "numerical pain scale" is being abandoned in the US: Why? British Journal of Anaesthesia, 2018, 120 (3): 435-438)
- "To prevent further opioid epidemics we need to abandon the clinical outpatient use of pain intensity scores and redefine the medical necessity of pain treatment as less about the reduction in pain intensity and more about the capacity to pursue personally values activities." Sullivan MD, and Ballantyne JC. Mayo Clinic Proceedings. July 7, 2023

What Defines Good Pain Management?

- Patient report
- Significant-other report
- Reduction in Numerical Pain Rating
- Improvement in function
- MME/number of pills per day
- Practitioner comfort
- Adherence to a specific 'guideline'
- Absence of complaint

BZD: impact on cortical structure and function

- BZD: associated w/ accelerated reduction in total brain volume, e.g. hippocampus, amygdala, thalamus, regions involved in memory and mood regulation
- Chronic BZD: may reduce neuroplasticity, and the brain's ability to form new connections and adapt.
  Gallet, Q. et al. Benzodiazepine use and neuroimaging markers of Alzheimer's disease in nondemented older individuals: an MRI and 18F-Florbetapir PET study in the MEMENTO cohort. Neuropsychopharmacol. 47, 1114–1120 (2022). https://doi.org/10.1038/s41386-021-01246-5
- Benzodiazepine-induced neurological dysfunction (BIND) (Ritvo AD, et al. Long-term consequences of benzodiazepine-induced neurological dysfunction: A survey. PLoS One. 2023 Jun 29;18(6):e0285584. doi: 10.1371/journal .pone. 0285584.)
- Protracted Withdrawal Syndrome (PWD) (Ashton H. Protracted withdrawal syndromes from benzodiazepines. J Subst Abuse Treat. 1991; 8: 19-28).
- Protracted Absence Syndrome (PAS) (Manhapra et al 2018)

Post-op opioid use

- 900 patients filled a prescription
- Oxycodone: most commonly prescribed opioid (70%).
- 341 patients (28%) did not fill the prescription
- 191/900 (21%) did not take any of the medication.
- 252/900 (28%) did not know how to dispose of the unused opioid tablets
- Two studies found 73% and 77% patients did not secure unused opioids (Bicket et al, JAMA Surgery, 2017, August 2, published online)

Unpublished data. 2023

Opioids and Children: "1 Pill Can Kill"

- Hospitalizations for prescription opioid-related poisonings increased 165% for children ages 1-19, between 1997-2012
- Prescription opioid poisoning among adolescents 15-19 years increased by 176%
- The largest percentage increase poisonings was among the 1-4 year by 205%.
- Majority of the poisonings are unsupervised ingestions; of an opioid prescribed for a family member

Gaither et al. National trends in hospitalizations for opioid poisonings among children and adolescents, 1997 to 2012. JAMA Pediatrics. Published Online: October 31, 2016. doi:10.1001/jamapediatrics.2016.2154

Opioid Therapy: Be Aware of Opioid Induced…

Disorder	Incidence	MOA
Neurotoxicity	15% Ca pain study	Neuroexcitatory metabolites, e.g. morphine-6-glucuronide,oxymorphone-3-glucuronide; NMDA activity
Endocrinopathies	21-86%	Hypothalamic-pituitary-gonadal system
Hyperalgesia	Rare-27%	central glutaminergic system, spinal dynorphins, descending facilitation, genetic mechanisms, and decreased reuptake and enhanced nociceptive response
Immunosuppression	Unknown	impaired immune system function by affecting the H-P-A system, and suppressing natural killer (NK) cells

Ackerman WE, Paroxysmal opioid-induced pain and hyperalgesia. J Ky Med Assoc. 2006; 104:419-23
Marudhai S, et al. Long-term opioids linked to hypogonadism and the role of testosterone supplementation therapy. Cureus. 2020 Oct 5;12(10):e10813. doi: 10.7759/cureus.10813. PMID: 33173622; PMCID: PMC7645309.
Mazo M, Dawson KA. Opioid-induced neurotoxicity. Am J Nurs. 2013 Oct;113(10):51-6. doi: 10.1097/01.NAJ.0000435351.53534.83. PMID: 24067833.
Godwin B, et al. Identification and management of opioid-induced neurotoxicity in older adults. Can Fam Physician. 2022; ;68(4): 269-270..

Chronic Pain and Neuroimmune Interface

- Elevated levels of several cytokines found in the CSF of patients with LDH and those with DDD, indicating neuroimmune activation
- No of systemic inflammation and signs of a communication between CSF and serum.
- Systemic expression of inflammatory proteins suggest a hypoinflammatory environment
- Disease-specific associations were found between cytokines in CSF and back pain intensity.

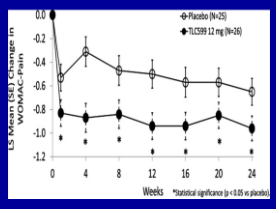
Rosenström A, et al Unraveling the neuroimmune interface in chronic pain—the association between cytokines in the cerebrospinal fluid and pain in patients with lumbar disk herniation or degenerative disk disease. PAIN, 2024;165(7): e65-e79, July 2024.

Nano Technology

Nanobodies (miniantibodies): blocks inflammation and reduces pain. Designed nanobodies to specifically inhibit P2X7 on immune cells reducing the activation of an an inflammatory response. The effect in humans in humans was 1,000 times more effectively than current drugs that target P2X7 (Koch-Nolte's et al. Science: Translational Medicine, 2016 (Nov.)

Intraarticular injections TLC599 (dexamethasone) 12 mg, produced significantly greater reduction in WOMAC pain and functional disability compared to placebo in patients with OA of the knee. The use of 18 mg was not superior to 12 mg

Hunter et al, TLC599 in patients with OA of the knee: a phase IIa, RCT, placebo-controlled, dose-finding study. Arthritis Res Ther. 2022 Feb 21;24(1):52. doi: 10.1186/



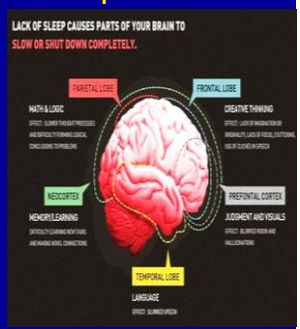
LDN/Ultra-LDN

Naltrexone (Oral)			
Crohn's Disease.	4.5 mg/day.	Favorable response in 89% of patients.	Smith et al. 2007
Irritable Bowel Syndrome (IBS).	0.5 mg/day.	Pain/symptom relief during first 2 months.	Kariv et al. 2006
Fibromyalgia.	4.5 mg/day.	Unknown, but anecdotal reports favorable.	SNAPL 2008
Neuropathic Pain (combined with methadone).	0.002 mg/day.	Improved analgesia at lower methadone dose.	Cruciani et al. 2003
+ Oxycodone (Oxytrex®) for osteoarthritis or chronic back pain.	0.002 mg/day.	Reduced opioid consumption and side effects, including resolution of opioid-induced constipation.	Chindalore et al. 2005; Webster et al. 2006
+ Hydrocodone (experimental).	0.25, 0.5, or 1.0 mg.	No beneficial effect.	Cantilena et al. 2004
+ Intrathecal morphine for chronic noncancer pain.	0.2 mg/day.	Reduced pain intensity, improved pain relief	Hamann and Sloan 2007
Opioid (methadone) tapering.	0.125 or 0.250 mg in multiple doses/day.	Reduced withdrawal symptoms and opioid craving compared with placebo.	Mannelli et al. 2006, 2008

Leavitt SB. Pain Treatment Topics, 2009
Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain Clin Rheumatol (2014) 33:451–459

Pain and Sleep

- Insomnia: 9-15% general population; comorbid w/pain 53-88%
- Symptoms: sleep onset, frequent awakening, early morning awakening, non-restorative sleep
- Sleep impairments:
  a) better predictor of pain then pain is of sleep impairment
  b) contributes to development and maintenance of chronic pain
  c) <5hrs 20% greater to be Dx with a chronic disease
  d) cognitive decline in 51 yrs+
  e) increase risk of suicide
- Sleep Apnea!!!



Ford & Kamerow, JAMA.1989, 262, 1479-84. Raymond I et al. Pain. 2001Finan et al, J Pain, 2013, 14(12):Tang et al., J Sleep Res., 2007. 16, 213-18. Smith et al., J Beh Med, 2009, 23, 1-13. Sabia S., et al PLOS, Medicine, 2022. 10.1371/journal.pmed.1004109. Zaheed, A.B., et al Sleep, 2022 zsac262, https://doi.org/10.1093/sleep/zsac262

Chronic Pain: Elderly & Cognitively Impaired

Altered:

- Central processing: altered functional connectivity and impaired contextual appraisal
- Expression
- Affective response
- Response to opioids: disruption of expectancy due to cognitive impairment (Benedetti et al. Pain, 2006; Cole et al. Eur J Pain, 2011)
- Homeostenosis: impaired ability to compensate/adapt (Karp et al, Brit J Anes, 2008, 101)
- Consequence: increased mortality and dementia (Domenichiello AF, Ramsden CE. Prog Neuropsychopharmacol Biol Psychiatry. 2019 ;93:284-290.

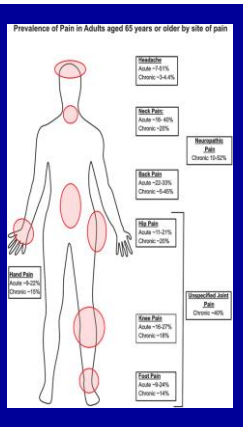
Chronic Pain in Elderly: Beliefs and Fears

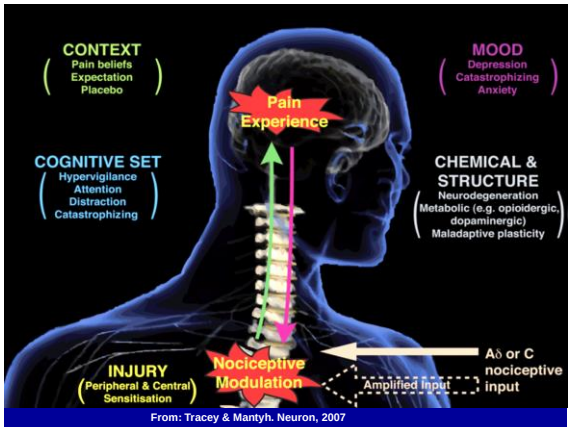
Pain is a normative part of aging.

Develop fatalistic attitudes about enduring pain and dysphoria.

Reasons for not 'speaking out':

(1) Fear of being labeled a bad patient
(2) Pain may signify serious illness
(3) Fear of addiction
(4) Pain medications need to be saved 'for the end'
(5) Fear of lose of independence
(6) Anxiety over additional diagnostic tests and the cost of such tests





From: Tracey & Mantyh. Neuron, 2007

Regarding the Use of Opioids

Courtesy: Dr. David McLain

Pain is not an opioid deficiency

Life is not a chemical deficiency

Don't say yes if you cannot say no

Be the clinician your patient needs; not just the one they want

Be a responsible prescriber, and not a 'vending machine'

Thank You