Supplementary Pre-Course Materials

for

Prescribing and Pain Management

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§8. Medical Record Documentation in Pain Management

NOTE: The exam questions will be from sections 2-8.

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OPTIONAL MATERIALS

§9. Apps for Chronic Pain and Other Chronic Health Issues

§10. CURES 2.0 State of California - Click Here to View Article
Prescriber and Dispenser User Guide

§11. About CDC's Opioid Prescribing Guideline | Opioids | CDC

https://www.cdc.gov/opioids/providers/prescribing/guideline.html

§12. Videos – To view the video, click on the title.

1. Video - Pain Evaluation, Documentation and Assessment
2. Video - Pain Rx - Initiating Treatment and Pharmacology
3. Video - Pain Rx & Drug Addiction
4. Video - Federal Regulation of Opioids and Controlled Substances
5. Video - Pain Rx & Compliance with State Licensing Board Rules
6. Video - Pain Rx & Prescription Drug Monitoring and State Law

§1. Resources for Pain Management:

1. NIH National Center for Complementary and Integrative Health
2. The Pain Management Best Practices Inter-Agency Task Force
3. NIH Pain Consortium
4. U.S. National Library of Medicine
5. Unused Medicine Disposal
6. Prescription Drug Monitoring Programs
7. SAMHSA Opioid Treatment Program Directory

Opioids

The misuse of prescription opioids and use of heroin is one of the most significant public health issues in the United States. Opioid abuse claims more lives than motor vehicle crashes. Providing access to effective care may prevent misuse and the consequences, such as overdose. Our researchers study the causes of the crisis and the effectiveness of the programs and policies implemented in response.

Categories Related to Opioids

- Opiate or Opioid
- Alcohol
- Nicotine
- Illicit Stimulants
- Alcohol Abuse
- Underage Drinking
- Pain Relievers
- Prescription Drugs
- Drug Use Trends
- Marijuana
- Sedatives
- Suicide
- Benzodiazepines
- Methadone
- Heroin

§2. The 2022 CDC Guideline for Prescribing Opioids for Chronic Pain

In January 2020, an advisory CDC Opioid Workgroup (OWG) appointed by the Board of Scientific Counselors (BSC) of the CDC to oversee and evaluate a new draft of the revised CDC guidelines.

On July 16, 2021, the Board of Scientific Counselors (BSC) of the CDC National Center for Injury Prevention and Control (NCIPC) held a public meeting to review the process and progress in an ongoing revision of the to review findings by the CDC OWG.

The new CDC guidelines are expected in 2022 and include 12 draft recommendations as follows:

(1) ACUTE PAIN

"Nonopioid therapies are preferred for many common types of acute pain. Clinicians should consider opioid therapy for acute pain only if benefits are anticipated to outweigh risks to the patient." (Recommendation Category: A; Evidence Type: 3)

(2) SUBACUTE AND CHRONIC PAIN

"Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients known risks and realistic benefits of opioid therapy, should establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. If opioids are used, they should be combined with other therapies as appropriate." (Recommendation Category: A, Evidence Type: 3)

(3) IMMEDIATE-RELEASE AND EXTENDED-RELEASE OPIOIDS

"When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids." (Recommendation Category: A and Evidence Type: 3)

(4) OPIOID-NAÏVE PATIENTS

"When opioids are started for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage. If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to > 90 MME/day." (Category A, Evidence type 3)

(5) LEGACY PATIENTS ON OPIOIDS

"For patients already receiving higher opioid dosages (eg, >90 MME/day), clinicians should carefully weigh benefits and risks and exercise care when reducing or continuing opioid dosage. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids." (Recommendation Category: A and Evidence Type: 4)

(6) THE 3-7 DAY PRESCRIPTION LIMIT

"When opioids are used for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. One to three days

or less will often be sufficient; more than seven days will rarely be needed." (Recommendation Category: A and Evidence Type: 4)

(7) ONGOING OPIOID THERAPY

"Clinicians should continue opioid therapy for subacute or chronic pain only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for subacute or chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently." (Recommendation Category: A, Evidence Type: 4)

(8) OPIOID RISKS, OVERDOSE, AND RELATED HARMS

"Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss with patients. Clinicians should incorporate into the management plan, strategies to mitigate risk, including offering Naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use, are present." (Recommendation Category: A, Evidence Type: 4)

(9) DRUG MONITORING

"Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for acute or chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months." (Recommendation Category: A, Evidence Type: 4)

(10) DRUG TESTING

"When prescribing opioids for chronic pain, clinicians should use drug testing before starting opioid therapy and consider drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs." (Recommendation Category: B, Evidence Type: 4)

(11) BENZODIAZEPINES AND OPIOID USE DISORDER: DRUG-DRUG INTERACTIONS

"Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants." (Recommendation Category: A, Evidence Type: 3)

(12) PATIENTS WITH OPIOID USE DISORDER

"Clinicians should offer or arrange treatment with medication for patients with opioid use disorder." (Recommendation Category: A, Evidence Type: 2)

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§3. Drug prescribing[1]

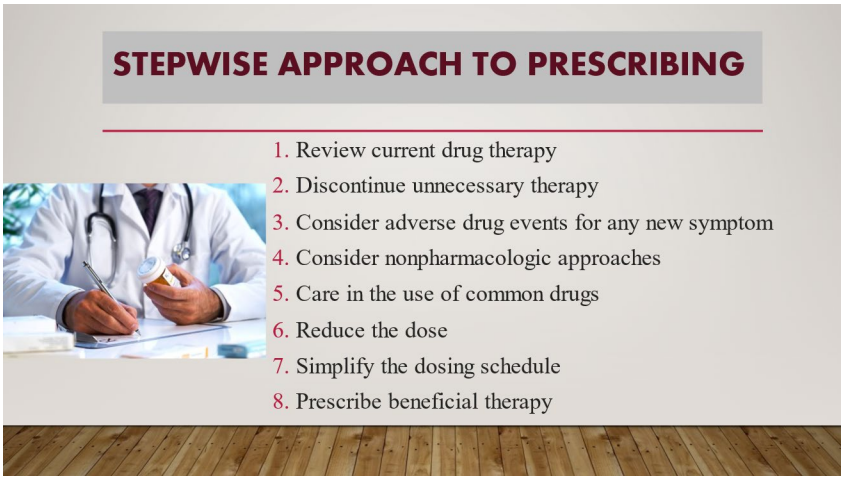
An essential part of caring for patients is:

(a) optimizing drug therapy; and
(b) avoiding adverse drug events (ADEs).

Prescribing medications is a process. It includes:

i. deciding that a drug is indicated,
ii. choosing the best drug, based on knowledge, expertise, and judgment,
iii. determining a dose and schedule appropriate for the patient's physiologic status,
iv. monitoring for effectiveness and toxicity,
v. educating the patient about expected side effects, and
vi. indications for seeking consultation.

After prescribing a new drug, any new symptom should be considered drug-related until proven otherwise.



In 2016, a study was conducted by Saraf and co-authors[2] on a sizeable sample of Medicare beneficiaries who were discharged from an acute hospitalization to a skilled nursing facility.

- The authors reported that the ***patients were prescribed an average of 14 medications***, and
- Over one-third of the patients had medication side effects that could exacerbate their underlying geriatric problems.

[1] https://www.uptodate.com/contents/drug-prescribing-for-older-adults/print (last updated: May 27, 2022.)
[2] Saraf AA, Petersen AW, Simmons SF, et al. Medications associated with geriatric syndromes and their prevalence in older hospitalized adults discharged to skilled nursing facilities. J Hosp Med 2016; 11:694.

3. *Herbal Remedies*

In addition to prescribed medications, the ***use of herbal or dietary supplements*** by patients has dramatically increased (e.g., ginseng, ginkgo biloba extract, and glucosamine).

Many patients obtain information about herbal products from the Internet. The most widely used herbal supplements are ginkgo biloba, St. John's wort, echinacea, ginseng, garlic, saw palmetto, kava, and valerian root.

Often, patients do not routinely volunteer information about their herbal remedies, and clinicians do not usually question patients about the use of herbal or dietary supplements.

Herbal medicines may interact with prescribed drug therapies and lead to adverse events. This underscores the importance of ***routinely*** questioning patients about the use of unconventional therapies.

For example,

1. ginkgo biloba extract taken with Coumadin (warfarin), causes an increased risk of bleeding, and
2. St. John's wort taken with serotonin-reuptake inhibitors, increase the risk of serotonin syndrome in older adults.

4. *The Serotonin or 5-HT (5-hydroxytryptamine) Syndrome*

Serotonin (5-HT) helps regulate mood and social behavior, appetite, digestion, sleep, memory, and sexual drive. It is commonly thought to be a neurotransmitter, but some consider it to be a hormone.

The FDA has asked drugmakers to add warning labels about the risk of serotonin syndrome.

The Serotonin syndrome is when the body has an excess of the neurotransmitter serotonin or 5-hydroxytryptamine; 5-HT. This can lead to extreme nerve cell activity and dangerous symptoms, including:

- Confusion, agitation or restlessness, changes in BP or temperature.
- Tachycardia, shivering and goose bumps, sweating, and dilated pupils.
- Headache, nausea, vomiting, diarrhea.
- Muscle twitching and loss of muscle control; and
- In severe cases, it causes High fever, Seizures, and Passing out.

The cause of serotonin syndrome is usually medications, especially certain antidepressants. The patient might be at higher risk when taking two or more drugs and/or dietary supplements that increase serotonin levels.

(1) The most prescribed class of antidepressants are the SSRIs (Selective serotonin reuptake inhibitors). They act by raising the 5-HT or serotonin levels. They include:

- Citalopram (Celexa)
- Escitalopram (Lexapro)
- Fluoxetine (Prozac)
- Fluvoxamine (Luvox)
- Paroxetine (Paxil)
- Sertraline (Zoloft)

(2) **The SNRIs (Serotonin and norepinephrine reuptake inhibitors),** is another class of antidepressants which include:

- desvenlafaxine (Khedezla),
- desvenlafaxine succinate (Pristiq),
- duloxetine (Cymbalta),
- levomilnacipran (Fetzima), and
- venlafaxine (Effexor)

(3) **Monoamine oxidase inhibitors (MAOIs),** antidepressants include

- isocarboxazid (Marplan),
- phenelzine (Nardil),
- tranylcypromine (Parnate), and
- transdermal selegiline (EMSAM)

(4) **Antidepressants that affect multiple serotonin receptors,** such as vilazodone (Viibryd) and vortioxetine (Trintellix)

(5) **Other drugs that increase serotonin are:**

1. **Buspirone (BuSpar),** to treat anxiety disorders
2. **Trazodone (Desyrel),** for depression or insomnia
3. **Migraine treatments such as**
   almotriptan (Axert),
   naratriptan (Amerge),
   rizatriptan (Maxalt),
   sumatriptan (Imitrex), and
   zolmitriptan (Zomig)
4. **Certain pain medications, especially opioids and related medications** including
   fentanyl (Sublimaze, Fentora), fentanyl citrate (Actiq),
   meperidine (Demerol), pentazocine (Talwin), and tramadol (Ultram)
5. **Dextromethorphan,** a cough suppressant found in many over-the-counter and prescription cough medicines or cold medicines.
6. **Certain medications for nausea,** such as granisetron (Kytril), metoclopramide (Reglan), and ondansetron (Zofran)

(6) Some recreational drugs, such as LSD and cocaine, and dietary supplements, including St. John's wort and ginseng, can also cause serotonin syndrome when you take them with antidepressants.

Without treatment, the serotonin syndrome can cause seizures, kidney failure, trouble breathing, coma, and death.

No single diagnostic test is available to diagnose the serotonin syndrome. There is the medical history -- including your use of medications, supplements, and recreational drugs -- and physical exam. Lab tests are ordered to rule out other health conditions that can look like serotonin syndrome, such as tetanus, sepsis, encephalitis, or heatstroke.

The patient may need to stay in the hospital to treat the symptoms and monitor recovery.

Removing the drug that caused the serotonin syndrome is crucial, along with supportive treatment.

In severe cases, cyproheptadine (Periactin) helps decrease the production of serotonin in the body.

5. ***Polypharmacy***

Polypharmacy is defined as the use of 5-10 medications by a patient. Most commonly, it refers to prescribed medications. But it is important to also consider the number of over the counter and herbal/supplements used.

Problematic polypharmacy is defined as the use of multiple medications in a way that is not considered to be appropriate.

- About 20 percent of Medicare beneficiaries have five or more chronic conditions and 50 percent receive five or more medications.
- Among ambulatory older adults with cancer, 84 percent were receiving five or more and 43 percent were receiving 10 or more medications, in one study.

The use of greater numbers of drug therapies has been independently associated with an:

- increased risk for an adverse drug event (ADE), irrespective of age,
- increased risk of hospital admission, and
- decreased physical and cognitive capability.

The reasons include:

Metabolic and drug clearance issues.
Drug-drug interactions.
Polypharmacy is an independent risk factor for hip fractures in older adults.
Polypharmacy increases the possibility of "***prescribing cascades***". A prescribing cascade develops when an ADE is misinterpreted as a new medical condition and additional drug therapy is then prescribed to treat this medical condition (see 'Prescribing cascades' below). Prescribing cascades are part of the definition of problematic polypharmacy.

Use of multiple medications can lead to problems with adherence, especially in older adults.

6. Inappropriate Medications

i. Anticholinergic medications are associated with multiple adverse effects, including memory impairment, confusion, hallucinations, dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, tachycardia, and increased risk of developing community-acquired pneumonia and acute glaucoma.
ii. Between 2005 and 2009, in the U.S., 23.3% of community-dwelling persons over 65 years with dementia were prescribed medications with clinically significant anticholinergic activity.
iii. In a population study of 6912 adults 65 years and older, those taking anticholinergic drugs were at increased risk for cognitive decline and dementia and risk decreased with medication discontinuation.
iv. In a population of 3434 adults age 65 and older in one health care setting, who had no baseline dementia and who were followed for 10 years, the risk of dementia and Alzheimer's disease increased in a dose-response relationship with use of anticholinergic drug classes (primarily first-generation antihistamines, tricyclic antidepressants, and bladder antimuscarinics).
v. In another population of 13,004 individuals aged 65 and older, use of anticholinergic medications was also shown to be associated with greater decline in cognition as measured by the Mini-Mental State Examination. In addition, anticholinergic medication use was associated with increased mortality over a two-year period after adjustment for multiple factors, including comorbid health conditions.
vi. At usual doses, AA is most significantly elevated for amitriptyline, atropine, clozapine, dicyclomine, doxepin, L-hyoscyamine, thioridazine, and tolterodine [54].
vii. AA also was increased for chlorpromazine, diphenhydramine, nortriptyline, olanzapine, oxybutynin, and paroxetine.
viii. Adverse drug reactions (ADRs) other than AA should also be taken into account in weighing the clinical benefits of possible substitutions (e.g., dyskinesias and sedation with haloperidol and perphenazine).

7. How does one assess the quality of prescribing practices and medication?

a) The Drug Burden Index. This has been modelled incorporating drugs with anticholinergic or sedative effects, total number of medications, and daily dosing. An increased drug burden for anticholinergic and sedative medications was associated with impaired performance on mobility and cognitive testing in high-functioning community-based older adults. Zolpidem was implicated in 21 percent of emergency department visits for adverse drug events (ADEs) related to psychiatric medication among adults 65 years and older.

Total number of medications was not associated with impaired performance when sedatives and anticholinergics were excluded. A high Drug Burden Index has been correlated with increased risk for functional decline in community dwellers and with increased risk of falls in residents in long-term care facilities.

Multiple scales in addition to the Drug Burden Index have been developed to qualify the AA of medications. In one study, a higher score on each of nine different anticholinergic burden scales was associated with increased risk for hospitalization and length of stay, falls, and medical utilization.

b) In older patients, the ***Beers criteria*** are the most widely used in the U.S. to assess inappropriate drug prescribing. The criteria are a list of medications considered potentially inappropriate for use in older patients, mostly due to high risk for adverse events.

Medications are grouped into five categories:

a) Drugs potentially inappropriate in most older adults,
b) Drugs that should typically be avoided in older adults with certain conditions,
c) Drugs to use with caution,
d) Drug-drug interactions, and
e) Drug dose adjustment based on kidney function.

The most recent update of the Beers criteria was in 2019, by the American Geriatrics Society

Several studies using older versions of the Beers criteria have identified that use of drugs identified as "inappropriate" was widespread in the United States, Canada, and Europe. For example, in a sample of community-dwelling older adults in the United States, 43 percent used at least one medication that would be deemed potentially inappropriate by the criteria, with nonsteroidal anti-inflammatory drugs (NSAIDs) being the most common.

Some of the inappropriate drug therapies identified on the Beers list are available as over-the-counter products. This reinforces the need to always consider over-the-counter drug therapies when reviewing a patient's medications and to educate individuals on potential problems that can arise from the use of over-the-counter preparations.

The Beer's criteria have been used to monitor quality of care for older adults. Studies of earlier versions of the Beers criteria found that while the criteria did predict some adverse outcomes, results were mixed.

c) **Other criteria sets** — The ***Screening Tool of Older Person's Prescriptions (STOPP) criteria***, another tool for identifying inappropriate prescribing, was introduced in 2008 and updated in 2015. The 2003 Beers criteria have been compared with the Screening Tool of Older Person's Prescriptions (STOPP); STOPP and Beers

criteria overlapped in several areas, but earlier versions of the Beers criteria used in this comparison contained some drugs no longer in common use, and STOPP includes consideration of drug-drug interactions and duplication of drugs within a class.

In two studies, STOPP identified a significantly higher proportion of older people requiring hospitalization because of a medication-related adverse event than did the 2003 Beers criteria. In a cluster randomized trial in Ireland, presenting attending physicians with potentially inappropriate medications based on the STOPP/START (Screening Tool to Alert doctors to the Right Treatment) criteria reduced the number of adverse drug events and medication costs during the index hospitalization, but did not reduce length of stay.

d) The ***FORTA (Fit FOR The Aged) list*** identifies medications rated in four categories (clear benefit; proven but limited efficacy or some safety concerns; questionable efficacy or safety profile, consider alternative; clearly avoid and find alternative) with ratings based on the individual patient's indication for the medication. The tool, developed in Germany, has undergone consensus validation with a panel of geriatricians, but studies of its impact on clinical outcomes are ongoing.

e) **Health care financing administration** — The Centers for Medicare and Medicaid Services drug utilization review criteria target eight prescription drug classes (digoxin, calcium channel blockers, ACE inhibitors, H2 receptor antagonists, NSAIDs, benzodiazepines, antipsychotics, and antidepressants) and focus on four types of prescribing problems (inappropriate dose, inappropriate duration of therapy, duplication of therapies, and potential for drug-drug interactions). In one study, 19 percent of 2508 community-dwelling older adults were using one or more medications inappropriately; NSAIDs and benzodiazepines were the drug classes with the most potential problems.

8. ***Assessing Care of Vulnerable Elders project*** — Another expert panel has identified quality indicators for appropriate medication use as part of the Assessing Care of Vulnerable Elders (ACOVE) project. These indicators begin with practical suggestions on how to improve prescribing practices:

   (1) Document the indication for a new drug therapy
   (2) Educate patients on the benefits and risks associated with the use of a new therapy
   (3) Maintain a current medication list
   (4) Document response to therapy
   (5) Periodically review the ongoing need for a drug therapy

   In addition, these indicators specify drug therapies that either should not be prescribed for older adults or that warrant careful monitoring after they have been initiated.

9. ***Drug-drug interactions*** — Older adults are particularly vulnerable to drug-drug interactions because they often have multiple chronic medical conditions requiring

multiple drug therapies. The risk of an adverse event due to drug-drug interactions is substantially increased when multiple drugs are taken.

- Digoxin toxicity is 12 times more likely for patients who had been started on clarithromycin.
- Hyperkalemia was 20 times more likely for patients who were treated with a potassium-sparing diuretic.

Care must be taken when prescribing any medication, especially for the older individual, to review existing medications and consider potential drug interactions.

Long-term care residents are at a particularly high risk for developing adverse events. The average United States nursing home resident uses seven to eight different medications each month, and about one-third of residents have monthly drug regimens of nine or more medications.

Antipsychotic medications, used for the management of the behavioral and psychological symptoms of dementia, are among the drugs most frequently associated with adverse events in long-term care facilities. Psychotropic medications are associated with an increased risk for falls.

10. PEARLS:

- Maintain an accurate list of all medications that a patient is currently using. This list should include the drug name (generic and brand), dose, frequency, route, and indication.
- Advise periodic "brown-bag check-ups." Instruct patients to bring all pill bottles to each medical visit; bottles should be checked against the medication list.
- Patients should be made aware of potential drug confusions: sound-alike names, look-alike pills, and combination medications.
- Patients should be informed of both generic and brand names, including spelling, as well as the reasons for taking their medications. This may prevent unnecessary confusion when drugs are inconsistently labeled. As an example, a patient may be unaware that digoxin (generic) and Lanoxin (brand) are the same therapy.
- Medication organizers that are filled by the patient, family member, or caregiver can facilitate compliance with drug regimens. Blister packs for individual drugs, prepared by the pharmacist, can also be helpful in ensuring that patients take their medications correctly.
- Community pharmacists are an important resource and can play a key role in working with older adults to reduce medication errors.

STEPWISE APPROACH TO PRESCRIBING

- **Review current drug therapy** — Periodic evaluation of a patient's drug regimen is an essential component of medical care for an older person.

- **Discontinue unnecessary therapy** — Clinicians are often reluctant to stop medications, especially if they did not initiate the treatment and the patient seems to be tolerating the therapy.
- **Consider adverse drug events for any new symptom** — Before adding a new therapy to the patient's drug regimen, clinicians should carefully consider whether the development of a new medical condition could be the presentation of an atypical ADE to an existing drug therapy.
- **Consider nonpharmacologic approaches** — Some conditions in older adults may be amenable to lifestyle modification in lieu of pharmacotherapy.
- **Care in the use of common drugs** — Some commonly prescribed drugs may result in increased toxicity in older adults.
- **Reduce the dose** — Many ADEs are dose-related. When prescribing drug therapies, it is important to use the minimal dose required to obtain clinical benefit.
- **Simplify the dosing schedule** — When multiple medications are required, greater regimen complexity will increase the likelihood of poor compliance or confusion with dosing.
- **Prescribe beneficial therapy** — Patients must be informed about the reason to initiate a new medication and what the expected benefits are.

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§4. Use of AI in Drug Discovery and Development[3]

AI (Artificial Intelligence) is a technology-based system involving various advanced tools and networks that can mimic human intelligence but not replace human physical presence completely. AI has several subsets, including:

(1) Machine Learning (ML)which uses algorithms that can recognize patterns within a set of data that has been further classified; and
(2) Deep Learning (DL), which engages artificial neural networks (ANNs) that mimics the transmission of electrical impulses in the human brain. ANNs have subtypes, including multilayer perceptron (MLP) networks, recurrent neural networks (RNNs), and convolutional neural networks (CNNs), which utilize either supervised or unsupervised training procedures.

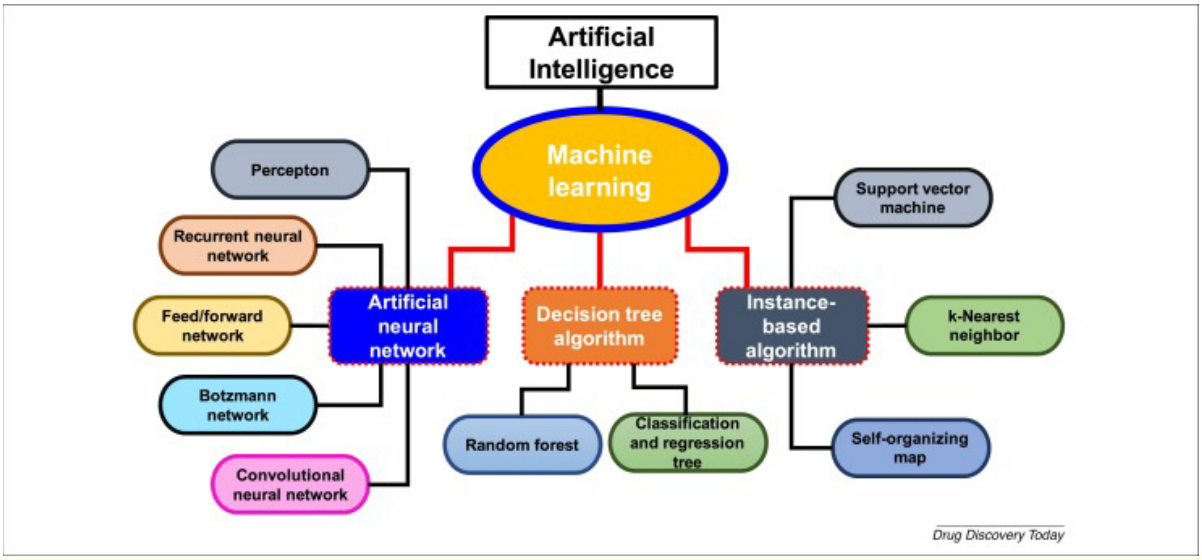
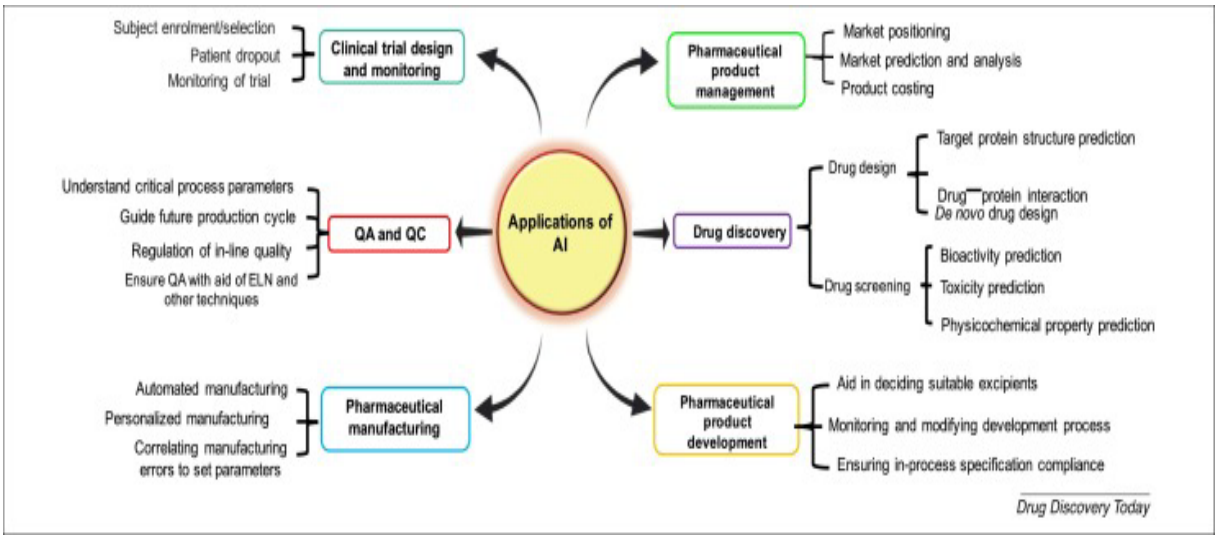


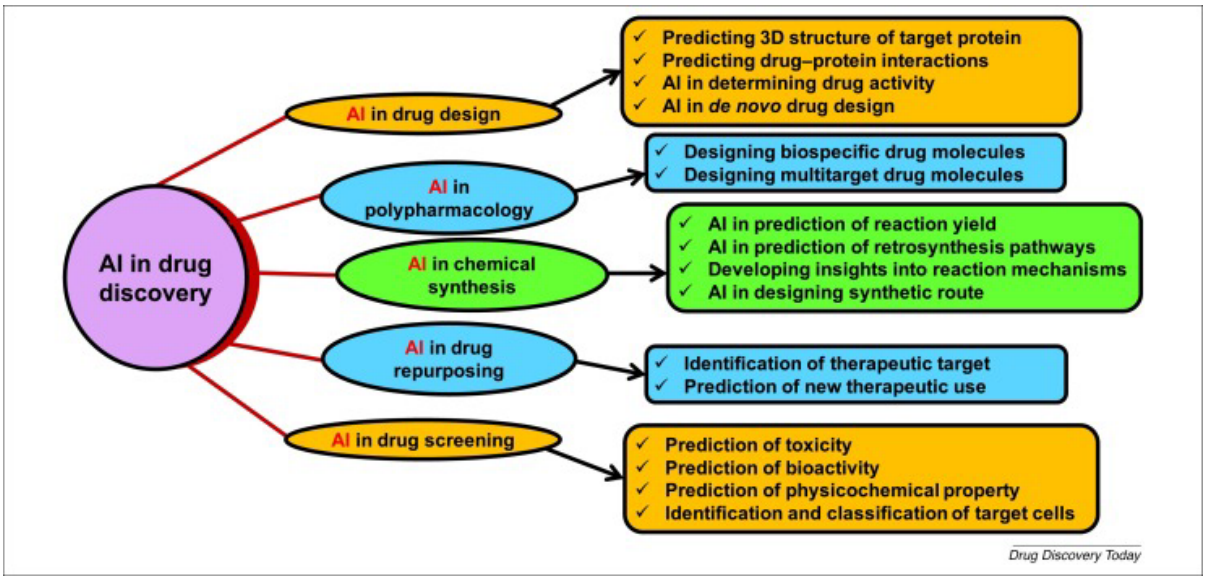
Figure 1
Method domains of artificial intelligence (AI). This figure shows different AI method domains along with their subfields that can be implemented in different fields drug discovery and development.

AI can assist in decision making; determine the right therapy for a patient, including personalized medicines; and manage the clinical data generated and use it for future drug development; create analytical roadmaps that help marketing executives. (See Figure 2)

[3] Drug Discov Today. 2021 Jan; 26(1): 80–93. Published online 2020 Oct 21. doi: 10.1016/j.drudis.2020.10.010



AI can recognize chemical compounds and provide a quicker validation of the drug target and optimization of the drug structure design, including drug design, chemical synthesis, drug screening, polypharmacology, and drug repurposing. Different applications of AI in drug discovery are depicted in Figure 3 .



The process of discovering and developing a drug (Phase I) can take over a decade and costs US$2.8 billion on average. Nine out of ten therapeutic molecules fail Phase II clinical trials and regulatory approval.

(1) Drug Physicochemical Properties

The physicochemical properties, such as solubility, partition coefficient (logP), degree of ionization, and intrinsic permeability of the drug, indirectly affect its pharmacokinetics properties and its target receptor family and, hence, must be considered when designing a new drug. Different AI-based tools can be used to predict physicochemical properties. AI has a significant role in the development of a drug, to predict not only its desired physicochemical properties, but also the desired bioactivity. DL approaches have shown improved performance compared with ML because they apply network-based methods that do not depend on the availability of the 3D protein structure

(2) Drug Efficacy and Prediction of Toxicity

The efficacy of drug molecules depends on their affinity for the target protein or receptor. Drug molecules that do not show any interaction or affinity towards the targeted protein will not be able to deliver the therapeutic response. By contrast, in similarity-based interaction, the similarity between drug and target (receptor) is considered, and it is assumed that similar drugs will interact with the same targets.

The prediction of the toxicity of any drug molecule is vital to avoid toxic effects. Cell-based in vitro assays are often used as preliminary studies, followed by animal studies to identify the toxicity of a compound, increasing the expense of drug discovery.

For selective targeting of disease, it is vital to predict the structure of the target protein to design the drug molecule. AI can assist in structure-based drug discovery by predicting the 3D protein structure because the design is in accordance with the chemical environment of the target protein site.

Drug–protein interactions have a vital role in the success of a therapy. Various AI methods have been useful in the accurate prediction of ligand–protein interactions, ensuring better therapeutic efficacy. The ability of AI to predict drug–target interactions is also used to assist the repurposing of existing drugs and avoiding polypharmacology. Drug–protein interactions can predict the chances of polypharmacology, which is the tendency of a drug molecule to interact with multiple receptors producing off-target adverse effects. AI can design a new molecule based on the rationale of polypharmacology and aid in the generation of safer drug molecules.

(3) Drug Manufacture, Clinical Trials and Marketting

Modern manufacturing systems try to confer human knowledge to machines. The incorporation of AI in manufacturing can prove to be a boost for the pharmaceutical industry. Quality control tests on the products, as well as maintenance of batch-to-batch

consistency, require manual interference. AI can also be implemented for the regulation of in-line manufacturing processes to achieve the desired standard of the product.

Clinical trials are directed toward establishing the safety and efficacy of a drug product in humans for a particular disease condition and require 6–7 years along with a substantial financial investment. Drug failures can be reduced with the implementation of AI. The enrolment of patients takes one-third of the clinical trial timeline. Drop out of patients from clinical trials accounts for the failure of 30% of the clinical trials, creating additional recruiting requirements for the completion of the trial, leading to a wastage of time and money.

Based on the market analysis and cost incurred in the development of the pharmaceutical product, the company determines the final price of the product. The critical concept in applying AI to determine this price is harnessing its ability to mimic the thinking of a human expert to assess the factors that control the pricing of a product after its manufacture. Factors, such as expenditure during research and development of the drug, strict price regulatory schemes in the concerned country, length of the exclusivity period, market share of the innovated drug after a year before are patent expiry, price of the reference product, and price-fixing policies determine the price of branded and generic drugs.

Several combinations of drugs are approved and marketed to treat complex diseases, such as TB and cancer, because they can provide a synergistic effect for quick recovery. Combination drug delivery can be more efficient if backed up by data on the synergism or antagonism of drugs administered together.

Nanomedicines use nanotechnology and medicines for the diagnosis, treatment, and monitoring of complex diseases, such as HIV, cancer, malaria, asthma, and various inflammatory diseases.

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§5. Top 10 medication errors and hazards, according to medication safety group

Each year, 7,000 to 9,000 people in the United States die due to medication errors. Most errors occur at the ordering or prescribing stage because of a healthcare provider writing the wrong medication, wrong route or dose, or the wrong frequency. These mistakes account for nearly 50% of medication errors. They are pervasive problem, but they are often preventable.

Similar-looking products from different manufacturers can cause medication mix-ups.

- **Selecting the wrong medication after entering the first few letters of the drug name**

(1) When entering just the first few letters of a drug name, or a combination of the first few letters and the product strength, similar-looking drug names can pop up on the screen. This can result in selection errors by busy or hurried healthcare workers.
(2) For example, entering in the computer 'met' has often led to confusion between methylphenidate, methadone, metolazone, methotrexate, metformin, and metronidazole; and
(3) entering 'meth10' has led to confusion between methadone 10 mg and methylphenidate 10 mg, (for ADHD)
(4) With the increasing use of technology, this problem has increased in frequency. In fact, selection errors may now rival or exceed those made with handwritten orders.

- **Daily instead of weekly oral methotrexate for non-oncologic conditions**

  Up to 4 in 1,000 patients erroneously take methotrexate daily instead of weekly for non-oncologic conditions, according to an FDA analysis. Of these frequency errors, about one-half are made by healthcare providers who inadvertently prescribe, label, and/or dispense methotrexate daily when weekly is intended; the other half of errors are made by older patients who get confused about frequency, according to an ISMP report of methotrexate administration errors.

  "We encourage every healthcare provider to: 1) default to a weekly dosage regimen when entering electronic orders or prescriptions for oral methotrexate, 2) require an appropriate oncologic indication for all daily methotrexate orders, and 3) provide patient and family education about the importance of weekly administration," ISMP advised.

- **Zinc overdoses**

  In 2019, a 2-year-old child nearly received a fatal overdose of zinc that was 1,000 times stronger than the appropriate dose. The electronic pediatric parenteral nutrition (PN) template defaulted to "mg" dosing units instead of "mcg." So, the physician inadvertently prescribed 700 mg of zinc instead of 700 mcg. Even if the physician had noticed the error, he couldn't have corrected it to "mcg" because the mg dosing unit was hard coded into the template. To make matters worse, the order entry system didn't fire a warning alert for the 1,000-fold dosing error.

  Fortunately, the pharmacist at the compounding pharmacy noticed the large dose and contacted the hospital pharmacist to question the order. The error was identified, and the problem was corrected before any harm befell the child.

  "Critical dose warnings are not available for IV zinc and other trace elements used as parenteral nutrition additives, making errors more likely, particularly involving pediatric patients. Even 1,000-fold overdoses can happen," ISMP warned.

"We advise all healthcare providers to build, test, and heed maximum dose warnings in PN order entry systems, with a hard stop for critical zinc overdoses (eg, above 250 mcg/kg for pediatric PN)," the institute recommended. "ISMP also encourages drug information database vendors to create needed critical dose warnings for IV zinc and other trace elements, if they do not currently exist."

- **Using syringes for vinca alkaloids**

  Despite strong advocacy to always dilute vinca alkaloids in minibags, approximately 15% to 20% of US hospitals still use syringes to administer these drugs, mainly for pediatric patients, ISMP reported.

  Because vinca alkaloids continue to be erroneously administered by the intrathecal route, ISMP called upon the FDA to remove "administration by syringe" from the prescribing information in favor of minibag administration only.

  "Administration by syringe has been at the root of all reported errors associated with vinca alkaloids inadvertently given by the intrathecal route; thus, the most effective way to prevent patient harm is to supply all vinca alkaloids in minibags, avoiding the risk of confusion with syringes," the institute stated.

- **Unsafe labeling of prefilled syringes and infusions by compounders**

  Lack of standardized, FDA-reviewed labeling of prefilled syringes and premixed IV infusions prepared by 503b compounding pharmacies. The FDA doesn't hold compounding pharmacies to the same labeling standards as commercial manufacturers. As a result, these label variations can lead to confusion.

  For example, some compounders list the strength on labels as *per mL* rather than *per total volume* (as required on all FDA-approved labels).

  "Errors have occurred when the more prominent per mL strength is mistaken as the total amount of drug in the container," ISMP reported.

- **Wrong route errors with tranexamic acid**

  Multiple cases of accidental intraspinal injection of tranexamic acid have recently been reported—an error with a 50% mortality rate. Tranexamic acid can be mistaken for bupivacaine or ropivacaine because all three come in vials with blue caps. Also, they're often stored upright near each other with only the caps (not labels) visible.

  Practitioners are encouraged to obtain these drugs from various manufacturers to help differentiate the appearance of the vials. Also, make sure the labels on the vials are always visible. If possible, store tranexamic acid vials away from lookalikes, and add an extra label to vials noting the route of administration.

- **Unsafe use of IV push meds**

More work needs to be done to increase the safe administration of IV push injections. According to an ISMP analysis, three unsafe practices require substantial improvement:

- Only 22% of participants dispensed all adult IV push medications in a ready-to-administer form
- Only 23% had established and validated competency assessments for IV push medication preparation and administration
- Only 31% were confident that IV push medications were *not* diluted or reconstituted by drawing up the contents into a prefilled flush syringe of 0.9% sodium chloride.

Providers to follow its safe practice guidelines for IV push meds.

- **Unsafe overrides with automated dispensing cabinets**
  Unsafe practices and pitfalls that occur with automated dispensing cabinets (ADCs) continue to jeopardize patients.

  "One of the biggest challenges to the safe use of ADCs is the ease with which medications can be removed upon override, many times unnecessarily and without a perceived risk.

  Given the current widespread use of ADCs, healthcare organizations should review their safe use and identify their vulnerabilities. ISMP offers guidelines for using ADCs safely.

- **Misheard requests and communications**

  Verbal or telephone orders are still necessary for certain instances, such as prescribing a drug during an emergency procedure or providing a recommendation in a telephone consultation. Those oral communications can be misunderstood and result in errors if not verified.

  For example, a verbal order for antithrombin during surgery was mistaken as thrombin by the time it was communicated by phone to the pharmacy, and a recommendation for pralidoxime was mistaken as pyridoxine during telephone consultation with a poison control expert.

  When verbal orders *are* necessary, take extra steps to avoid confusion:
  - Repeat back the drug regimen (drug, dose, route, and frequency)
  - Spell the name of the drug
  - State the dose in single digits (eg, "one-five" for 15)

- **Lookalike product labeling**

Similar labeling and cap colors can make different products look alike, especially if they have similar names and dosages, are used for the same purpose, or are stored near one another. Plus, stylized graphics and prominent corporate names and logos can obscure a product's essential drug information.

Complicating the situation, humans tend to see what they want to see, rather than what is actually there (confirmation bias).

Examples of similar-looking products from the same manufacturer (eg, Alvogen's yellow-labeled vials of tranexamic acid, midazolam, labetalol, and vancomycin injection),

as well as similar-looking products from different manufacturers (eg, the green and white box designs for both Udenyca [pegfilgrastim-cbqv] and Prolia [denosumab]).

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§6. Criminalization of Medical Negligence

- The Food and Drug Administration receives more than **100,000 reports** of medication errors annually.
- About **four out of 10 Americans** (41%) have experienced or known somebody affected by a medical error.
- More than 7 million Americans are affected each year by medication errors, and the total annual cost is **$40 billion**.
- The estimated medication error rate is **between 8% and 25%**.

A. The Vaught Case - Nurse Criminally Negligent for Administering the Wrong Drug causing Patient Death

On Dec. 24, 2017, Charlene Murphey was admitted with a brain injury to Vanderbilt University Medical Center, where DeRonda Vaught worked as a nurse. To prepare her for a brain scan, Murphey was prescribed Versed, a benzodiazepine used to help patients relax.

The fatal medical error resulted from Vaught's interactions with an electronic medication cabinet, where nurses must enter the first part of the medication's generic name to withdraw a drug. Vaught attempted to withdraw Versed by typing "VE" into the system without realizing she should be searching for "midazolam," the generic name for Versed.

When the cabinet did not dispense Versed, Vaught triggered an override of the machine and withdrew vecuronium, a paralyzing medication, overlooking at least five warnings.

She administered the vecuronium and left Murphey to be scanned. Murphey died, and Vaught testified in a hearing that she was at fault because she had been "distracted" and "complacent."

The state board of nursing rescinded her nursing license, and Vaught was later charged with reckless homicide. She was acquitted of that charge but convicted of gross neglect of an impaired adult and negligent homicide, both lesser charges.

The role of safeguards played a major role in the Vaught trial. Vaught performed manual overrides when accessing the medication and saw, but did not act upon, several warning messages. The prosecution argued that this was so reckless that Vaught's behavior qualified as a homicide. In contrast, the defense and many nurses argued that the safeguards were so faulty that nurses routinely overrode them to access the correct drugs. State investigators found that Vanderbilt University Medical Center carried a "heavy burden of responsibility," but only Vaught faced criminal charges.

On May 13, 2022, RaDonda Vaught was sentenced to three years supervised probation with judicial diversion. The diversion option allows first-time offenders to have charges dropped and their records expunged once they successfully complete probation. Vaught faced a potential sentence of up to eight years imprisonment.

Davidson County Criminal Court Judge Jennifer Smith noted that there "have been consequences to the defendant." Although Vaught will not be imprisoned unless she violates the probation conditions, she was fired and lost her nursing license. Nurses and other healthcare workers attended the trial to protest the criminalization of nursing mistakes. After the verdict was announced, many applauded.

B. Administering medication safely requires five "rights":

- The right patient
- The right medication
- The right time
- The right dose
- The right route

What Can Be Done?

In addition to being sure to perform safety checks as individuals, healthcare providers can act to sustain a culture of safety to prevent medical errors. Here are six ways that can ensure a culture of safety and protect themselves.

1. If You See Something, Say Something

Doctors and Nurses can help prevent medical errors by speaking up if they notice a potential error in any of the five rights. This may sometimes require speaking up about a physician's or supervisor's potential error, but the ability to do so safely is a must for a true culture of safety.

2. Understand Your Limits

Healthcare workers are in a bind when they are overworked. While they know they need to rest to perform effectively, the nursing shortage has forced many to work even when they don't have enough rest.

If you're tired, put extra effort into checking and rechecking to avoid medical errors. Alert a supervisor if you're aware that you can't perform safely.

3. Report Issues with Systems That Require Overrides

The prosecution emphasized that Vaught performed several overrides to access the wrong medication during the trial. The defense countered that nurses routinely performed overrides to access correct medications.

Nurses, doctors, and pharmacists can address this issue by reporting false alarms and excessive overrides to superiors. They can document the number of overrides they must perform to access the correct medications. The Vaught trial may make administrators more aware of the importance of accurate warnings.

4. Pay Attention to Alerts and Alarms

During the Vaught trial, both parties agreed that Vaught saw several warnings as she prepared the incorrect medication. They disagreed on whether this was a case of a professional mistakenly ignoring "the boy who cried wolf" or reckless misconduct.

During the aftermath of this nurse trial, nurses should demand support for taking the extra time it takes to mentally process each alarm message and determine if it is valid or a false alarm. Like overrides, nurses can support safety by reporting false alarms and unnecessary alerts, both for the sake of efficiency and avoiding medical errors.

1. Advocate for Their Staff

Health administrators must ensure that their staff are equipped to prevent errors, both their own potential errors and those of others. This includes adequate staffing, tools, and education.

They must protect providers from retaliation for reporting errors and model speaking up when they notice potential medical errors.

2. Create an Environment of Accountability

Health care leaders can create a culture of accountability by ensuring that the organization's emphasis is on preventing medical errors at a systems and an individual level, rather than punishment after the fact, and that everybody is held responsible for preventing errors.

When nurses, doctors, and pharmacists believe that the culture of accountability permits them to speak up and that everybody takes responsibility for their actions, they feel they can speak up. They might also recommend improvements and act as a team to prevent medical errors.

3. Ensure Proper Staffing Ratios

Staffing levels affect how much time nurses can dedicate to safety checks and how likely they are to be distracted or functioning without enough rest. Studies consistently associate higher staffing ratios with better patient outcomes.

4. Incorporating Rounds and Debriefs as Daily Practices

Rounds and debriefs ensure that all providers know and communicate about patient conditions and prescribed treatments. They allow all participants to ask and answer questions in real time.

Rounds and debriefs also foster a habit of communication. They can develop professional relationships that help care providers communicate more effectively. Jean also urges providers to implement hourly huddles to share important information.

5. Encourage Writing and Reporting Incident Reports

Incident reports allow healthcare providers to understand what happened in the case of medical errors. Nurse leaders and administrators can use incident reports to look for patterns or potential failure points leading to medical errors.

6. Constantly Look for Ways to Improve Safety

Perform root cause analysis to foster a culture of safety by "creating hard stops and performing 'time outs' for all procedures."

A culture where nurses and all staff feel as though they will be listened to means that they will share ideas for improving safety.

7. Build Multidisciplinary Collaborations

Every team in a hospital has a role to play in preventing medical errors, not just clinicians. Human resources can support education, informatics teams can collect and analyze data, technology teams can carry out or recommend software and systems improvements, and clinicians at all levels can share ideas on improving safety and reducing medical errors.

C. Use of Large Doses of Fentanyl for Terminal Palliation of Pain and Suffering: Is it Murder?

On December 5, 2017, a 74-year-old patient was brought in critical condition to the emergency department of Mount Carmel Medical Center, a 136-year-old Catholic hospital owned by the Trinity Health system in Columbus, Ohio. He had diabetes and was previously hospitalized for treatment of a gangrenous foot. Upon arrival at the ER, he had acute renal failure and hypotension. He also had two cardiac arrests. The patient was intubated in the ER and sent to the ICU during the evening shift. He was placed under the care of William Husel, DO, the sole physician on duty in the ICU.

At approximately 9 PM, the family members were at the patient's bedside. The patient was unconscious and on the ventilator. Dr. Husel told the family that patient's organs were shutting down and he was brain damaged. He discussed the patient's "grim prognosis" and advised the patient's family that he had "minutes to live." Then Dr. Husel asked the family, "How would you want him to take his last breath: on the ventilator or without these machines?" The family agreed to ***palliative extubation***. The patient's ventilator was discontinued and the endotracheal tube was removed because he was expected to die.

Just prior to extubation, and to relieve the patient from pain and suffering, Dr. Husel verbally ordered the nurse to administer 1mg (1000 micrograms) of fentanyl, followed by 2 mg of hydromorphone, and 4 mg of midazolam.

The medical center's 2016 guidelines for IV administration of fentanyl specified a dosage range of 50 to 100 micrograms for relieving pain, and its 2018 guidelines reduced that to 25 to 50 micrograms. The nurses on duty skipped the standard non-emergency process of getting pre-approval from the pharmacist. Instead, they used the override function on the automated Pyxis system to withdraw the drugs from the dispensing cabinet and avoided pharmacist review. The nurse that administered the drugs to the patient said later that Dr. Husel told him the pharmacist had said, "It is okay." According to the pharmacy board report, the pharmacist wrote in the medical record system that he did not agree to the fentanyl order. However, his dissent came as the drugs were being administered and the breathing tube was being removed. The patient died approximately one hour after the ***palliative extubation***.

- ***About Dr. Husel***

  Dr. Husel was a former high school basketball star. He is married and his wife is a nurse.

  In 2013, after completing a residency and fellowship in critical care medicine and pain management at the Cleveland Clinic, Mount Carmel West hired him to work the late-night shift in its ICU. That was his first job as a full-fledged physician. He was a hard worker. He was popular with the ICU nurses and staff, who looked to him as a teacher and mentor. In 2014, Dr. Husel was chosen by his hospital colleagues as physician of the year. He was again nominated in 2018.

Before October 2018, there were no complaints about his care. When he applied for his medical license, he declared that in 1996, he pleaded guilty to a federal misdemeanor for improperly storing explosive materials. He received a 6-month sentence followed by supervision. Mount Carmel checked his background the previous 10 years and found nothing on him that would preclude his employment.

- ***Investigation, Discharge, License Suspension and Indictment of Dr. Husel***

  In 2017, Mount Carmel Medical Center launched a "Zero Harm" patient safety program, and medical staffers were supposed to report safety concerns up the chain of command. Dr. Husel's cases were reviewed from 2014-2018. There were 34 other ICU patients who were gravely ill who died minutes after receiving a single dose of 0.5mg or more of Fentanyl, often combined with other drugs while being removed from the ventilator and extubated.

  In December 2018, Mount Carmel concluded that the opioid dosages used by Dr. Husel were "significantly excessive and potentially fatal," and "went beyond providing comfort." Dr. Husel's employment was terminated, and he was reported to the Ohio Medical Licensing Board. His Ohio medical license was suspended.

  In June 2019, Dr. Husel was indicted and charged with 25 counts of murder. The prosecutors alleged that he ordered excessive or potentially fatal doses of fentanyl to be given by the nurses to patients under his care, and all of them died. *Dr. Husel is the only person facing criminal charges.* On August 28, 2019, Dr. Husel pleaded not guilty in court.

- ***Ripple Effect***

  1. In June 2019, after threatening to cut off Medicare and Medicaid payments to Mount Carmel, CMS accepted the hospital's correction plan, which (1) restricted use of verbal drug orders and prohibited Pyxis system overrides for opioids except in life threatening emergencies, (2) physicians must receive permission from a physician executive to order painkilling drugs that exceed hospital-set dosage parameters for palliative ventilator withdrawal, and (3) pharmacists must immediately report concerns about drug prescribing safety up the hospital pharmacy chain of command.
  2. Mount Carmel's CEO acknowledged that "processes in place were not sufficient to prevent these actions from happening." He stepped down as CEO in June 2019.
  3. The Chief Clinical Officer, and other physician, nursing, and pharmacy leaders, as well as two dozen nurses and two pharmacists had their employment terminated or entered into retirement. A total of 23 healthcare employees were fired.
  4. The ICU nurses that administered Fentanyl and the pharmacists faced disciplinary action, mostly license suspension for 1-3 years, for failing to inform their supervisors about the incident and preventing the use of those high drug dosages for the ***palliative extubation.*** *None of the nurses or pharmacists have been criminal charged.*
  5. Federal and State agencies cited the Mount Carmel for faults in its patient safety systems and culture causing a breakdown in oversight. Many of Dr. Husel's drug orders were given verbally instead of through the standard process of entering the orders into the electronic health record.
  6. Numerous wrongful death lawsuits were filed by the decedents' families against Mount Carmel and Dr. Husel alleging no record of anyone supervising Dr. Husel or monitoring

his care. Mount Carmel and Trinity have settled so-far a number of the lawsuits for nearly $20 million.

7. The Ohio Board of Pharmacy fined Mount Carmel $477,000 for pharmacy rules violations.
8. In December 2019, Dr. Husel sued the Mount Carmel Health System and its parent company, Trinity Health in Franklin County Common Pleas Court for *defamation* claiming that he was falsely accused of intentionally murdering 25 patients, and these statements were repeated on numerous occasions in "non-stop" press releases and other public statements. In 2014 and 2015, Mount Carmel Health responded to Dr. Husel's *defamation* lawsuit by saying:

   "Our priority at Trinity Health and Mount Carmel is the overall care and well-being of our patients and the health and wellness of the entire community we serve. All that we have done and continue to do reflects this commitment. Dr. Husel's defamation lawsuit has no merit, and we will defend our position vigorously."

9. Dr. Husel also sued Mount Carmel's parent company, Trinity Health, arguing that the company's insurance policy should pay for his criminal defense fees. The hospital rejected that claim in federal court filings and said that the allegations of murder are not insurable.

- ***Allegations, Defenses and Burden of Proof***

  The prosecution alleges that the doctor is a ***serial killer***. The defense counters that Dr. Husel's actions were compassionate and appropriate, and he never wanted to see any of his patients suffer, nor their family. His actions were in keeping with statutory immunity under the "dual effect' principle.

  The prosecutors must prove ***beyond reasonable doubt*** that (1) the drugs Dr. Husel ordered were what directly caused these critically ill patients to die, and (2) he intended to kill the patients. The prosecutor has to prove that the drugs hastened the patients' deaths, and by how much, and that the doctor is criminally responsible.

  The defense contends that physicians and other medical providers have certain legal protections under the double effect principle for administering drugs to patients for the purpose of relieving pain and suffering, even if the drugs hasten the patients' deaths, as long the intent was not to cause death and the drugs were properly used.

  In the civil cases, there is also the issue of how much a few more minutes, hours, days or weeks of life are worth in terms of monetary damages.

  On November 30, 2021, Dr. Husel's legal team argued in court that the 25 murder charges filed against him should be tossed out. They raised accusations of prosecutorial misconduct as a basis for their argument. They alleged that the prosecutor's office misled the grand jury and withheld evidence about a patient who received a larger dose of fentanyl than the other patients tied to the criminal case.

- ***Statements by ICU Nurses***

  Former Mount Carmel nurses testified in depositions that the amounts of drugs given to Dr. Husel's patients were not excessive. In response to a question about why a patient

would need 500 micrograms of fentanyl when their ventilator was being withdrawn, one of the nurses stated that in her view the dosage was not inappropriate. She stated at deposition, "So now he is going to be palliatively withdrawn. I am going to take away his breathing, take away the pressure that's keeping his lungs open. I am going to take all of that away and he is going to be on room air. He's going to suffocate to death. So 500 micrograms of fentanyl was not a large amount at all."

During their appearances before the state board of nursing, two nurses addressed the nursing board before their licenses were suspended for one year praised Dr. Husel, characterizing him as a doctor many nurses trusted because of his training and expertise in anesthesia and time spent working in Mount Carmel's intensive care unit. One of the nurses said: "I watched Dr. Husel go above and beyond to try and heal patients, and we fought for their lives." "I watched him perform miracles when other doctors couldn't or wouldn't try, and for these reasons, to hear and learn that he may have not been doing things within the standard of care has been very challenging to accept."

- ***Cause of Death and Trial***

  What exactly killed the patients remains in dispute. Mount Carmel acknowledged in 2018 and early 2019 that the patients "should not have been given excessive doses of fentanyl…" However, the probate court records state that since litigation was filed, the hospital has now "argued that fentanyl did not prematurely end (the patient's) life…"

  In January 2022, 11 counts of murder were dropped against Dr. Husel. But the judge allowed the prosecutors to present evidence that jurors could consider lesser offenses like reckless homicide in Dr. Husel's upcoming murder trial. The trial begins on February 14, 2022, in Columbus on 14 counts of murder.

- ***Is Dr. Husel a Serial Killer?***

  That is a question for the jury to decide. Serial killing is the rarest form of homicide making up no more than 1% of all homicides committed in the U.S. It occurs when an individual has killed three or more people who were previously unknown to him or her, with a 'cooling off' period between each murder.[4] The U.S. has more serial killers than any other place in the world. As of December 22, 2020, the total number of U.S. serial killers was 3,204.

  The FBI defines 'serial killings' as a series of three or more killings, not less than one of which was committed within the United States, having common characteristics such as to suggest the reasonable possibility that the crimes were committed by the same actor or actors.[5] The serial killer's behavior is generally regarded as unfathomable, decontextualized and sociopathic. Additionally, anonymity, the culture of celebrity enabled through the rise of mass media, and specific cultural frameworks of denigration, each provide key institutional frameworks, motivations and opportunity structures for analyzing such acts.

[4] https://www.crimeandjustice.org.uk/publications/cjm/article/social-study-serial-killers
[5] https://www.fbi.gov/stats-services/publications/serial-murder#two

- ***Deaths in ICU***

  Most patients dying in contemporary intensive care units succumb after limitation or withdrawal of life-sustaining therapy rather than during aggressive therapeutic care. Withdrawal of mechanical ventilatory support is often an integral component of the care of end-of-life care of critically ill, dying patients. Caring does not cease during these final moments of life. Compassionate care at the EOL includes offering opioids to control suffering from pain and dyspnea.

  In 2010, Mazer et al, reported that higher doses of morphine are associated with a longer time to death. The patients dying after ***palliative extubation*** received 10.6 mg/hour just before death. The mean time to death after terminal extubation was 152.7±229.5 minutes, and after extubation, each 1 mg/hour increment of morphine infused during the last hour of life was associated with a delay of death by 7.9 minutes (P=0.011). Dr. Husel worked in the ICU only and cared for critically ill patients.

- ***Supreme Court Decisions***

  The 'dual (or double) effect' principle means that sedation will help relieve pain and provide comfort, but it may also depress respiration and possibly lead to the patient's death. In 1997, the U.S. Supreme Court strongly approved aggressive palliation of pain in *Glucksberg*[6], and in *Vacco*.[7] The Court argued that it is "widely recognized that the provision of pain medication is ethically and professionally acceptable even when the treatment may hasten the patient's death, if the medication is intended to alleviate pain and severe discomfort, not to cause death." Justice O'Connor stated, "A patient who is suffering from a terminal illness and who is experiencing great pain has no legal barriers to obtaining medication, from qualified physicians, even to the point of causing unconsciousness and hastening death." Aggressive pain palliation is lawful and the state could not, consistent with the Constitution, prosecute a physician for causing a patient's death, where that death was a secondary consequence of aggressive pain management.

- ***Physicians' Attitudes***

  There are significant variations in physicians' attitudes and practice relating to withholding and withdrawing mechanical ventilatory support. In 1994, some 273 critical care physicians involved in ventilator management were surveyed regarding the clinical management of dying patients receiving mechanical ventilation.

  a) 15% almost never withdrew ventilators from dying patients foregoing life-sustaining treatment;
  b) 37% did so less than half the time.
  c) 26% believed there was a moral difference between withholding and withdrawing ventilators.

[6] 117 SCt 2258 (1997).
[7] 117 SCt 2293 (1997).

d) Of physicians who withdrew ventilators, 33% preferred terminal weaning, 13% preferred extubation. The reasons for preferring extubation included the directness of the action (72 percent), family perceptions (34 percent), and patient comfort (34 percent).
e) Morphine and benzodiazepines were used frequently by 74 percent (morphine) and 53 percent (benzodiazepines) of physicians when withdrawing ventilators; 6 percent used paralytics at least occasionally.

- ***Toxic Dose of Fentanyl***

  The toxic dose, LD_{50}, of Fentanyl in humans is unknown.[8] The lethal dose for the average person is estimated to be 2 mg.[9] The intravenous LD_{50} of Fentanyl in rats is 2.91mg/kg.[10] The calculated safety index (Odds Ratio of antinoceception/Odds Ratio of respiratory depression) for fentanyl is 1.20, suggesting that fentanyl has a low safety margin.

  In animals, the intravenous dose causing 50% of opioid-naive experimental subjects to die (LD_{50}) is 3 mg/kg in rats, 1 mg/kg in cats, 14 mg/kg in dogs, and 0.03 mg/kg in monkeys."[11] The LD_{50} in mice has been given as 6.9 mg/kg by intravenous administration, 17.5 mg/kg intraperitoneally, and 27.8 mg/kg by oral administration.[12]

  In 2021, Algera *et al*[13] published a pharmacokinetic-pharmacodynamic analysis of the respiratory effects of fentanyl in chronic opioid users and opioid-naïve subjects to quantify tolerance to respiratory depression. Apneic events occurred in opioid-naïve subjects after a cumulative fentanyl dose (per 70 kg) of 225 to 475 µg, and in 7 chronic opioid users after a cumulative dose of 600 to 1,800 µg. The authors stated that despite higher tolerance to fentanyl-induced respiratory depression, apnea still occurred in the opioid-tolerant population indicative of the potential danger of high-dose opioids in causing life-threatening respiratory depression in all individuals, opioid-naïve and opioid-tolerant.

- ***Dr. Husel's murder trial began on February 14, 2022.***

  The prosecution called 53 witnesses who ranged from family members of Husel's patients to medical doctors and nurses who worked with Husel. The defense team called just one witness, Dr. Joel Zivot, a physician from Emory University. The Jury found Dr. Husel not guilty.

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[8] *Vardanyan RS, Hruby VJ (March 2014). "Fentanyl-related compounds and derivatives: current status and future prospects for pharmaceutical applications". Future Medicinal Chemistry. **6** (4): 385–412. doi:10.4155/fmc.13.215. PMC 4137794. PMID 24635521*

[9] *"Fentanyl. Image 4 of 17". Drug Enforcement Administration*

[10] https://go.drugbank.com/drugs/DB00813

[11] *"Fentanyl Citrate Injection, USP" (PDF). US Food and Drug Administration.*

[12] *Yadav SK, Maurya CK, Gupta PK, Jain AK, Ganesan K, Bhattacharya R (June 2014). "Synthesis and biological evaluation of some novel 1-substituted fentanyl analogs in Swiss albino mice". Interdisciplinary Toxicology. **7** (2): 93–102. doi:10.2478/intox-2014-0013. PMC 4427721. PMID 26109885*

[13] https://pubmed.ncbi.nlm.nih.gov/32865832/

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§7. Methamphetamine-Associated Cardiomyopathy[14]

Methamphetamines are potent, highly addictive stimulants, the chronic use of which leads to multisystem dysfunction and disease. A major driver of methamphetamine-associated morbidity and mortality is the development of cardiomyopathy.

The cardiomyopathy associated with methamphetamine use is generally a dilated phenotype with reduced ejection fraction, although hypertrophic cardiomyopathy, stress-induced cardiomyopathy, and heart failure with preserved ejection fraction have all been described.

Despite the known association between methamphetamine use and cardiac dysfunction, the exact pathogenesis of methamphetamine-associated cardiomyopathy (MAC) remains poorly understood. Patients with MAC typically present with more severe disease at a younger age and with greater rates of multisystem involvement than patients with cardiomyopathy of other etiologies. Prompt recognition, assessment, and management of MAC is therefore essential.

Methamphetamines are illicit drugs of the amphetamine-type stimulant class that have been increasing in popularity, availability, and purity in recent decades. As a result, rates of methamphetamine-associated cardiomyopathy (MAC) are rising globally. MAC is associated with high rates of sudden cardiac arrest, late presentation, and poor outcomes.

The medical management of MAC includes anticipated challenges specific to methamphetamine users. Not only are patients with MAC more likely to present at a younger age and with multisystem disease than patients with cardiomyopathy of other etiologies, but there may also be significant behavioral, psychosocial, financial, and system-based challenges to providing the best medical care.

An individualized treatment plan that emphasizes methamphetamine abstinence as the foundation of therapy, as well as introducing optimal heart failure therapy and providing multidisciplinary support is likely to result in optimal outcomes.

Given the potential reversibility of MAC, institution of guideline-directed heart failure therapy and patient support for adherence to therapy and abstinence from methamphetamines should be energetically pursued.

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[14] Managing Methamphetamine Associated Cardiomyopathy (medscape.com)

§8. Medical Record Documentation in Pain Management

The physician who is treating pain patients should document the following:

1. Evaluation of the Patient

a. A complete medical history and physical examination **must** be conducted and documented in the medical record.
b. The medical record **must** document:
    i. The nature and intensity of the pain,
    ii. Current and past treatments for pain,
    iii. Underlying or coexisting diseases or conditions,
    iv. The effect of the pain on physical and psychological function, and
    v. History of substance abuse.
c. The medical record should document the presence of one or more recognized medical indications for the use of a controlled substance.

2. Written Treatment Plan

a. The written treatment plan should:
    i. State objectives that will be used to determine treatment success, such as pain relief and improved physical and psychosocial function, and
    ii. Should indicate if any further diagnostic evaluations or other treatments are planned.
b. After treatment begins, the physician should adjust drug therapy, if necessary, to the individual medical needs of each patient.
c. Other treatment modalities or a rehabilitation program may be necessary depending on the etiology of the pain and the extent to which the pain is associated with physical and psychosocial impairment.

3. Informed Consent and Agreement (Contract) for Treatment

a. The physician should discuss the risks and benefits of the use of controlled substances with:
    i. The patient,
    ii. Persons designated by the patient, or
    iii. With the patient's surrogate or guardian if the patient is incompetent.
b. The patient should receive prescriptions from one physician and one pharmacy where possible.
c. If the patient is determined to be at high risk for medication abuse or have a history of substance abuse, the physician should employ the use of a written agreement between physician and patient outlining patient responsibilities, including, but not limited to:

i. Urine/serum medication levels screening when requested;
ii. Number and frequency of all prescription refills; and
iii. Reasons for which drug therapy may be discontinued (i.e., violation of agreement).

4. Periodic Review

a. Based on the individual circumstances of the patient, the physician should review the course of treatment and any new information about the etiology of the pain.
b. Continuation or modification of therapy should depend on the physician's evaluation of the patient's progress.
c. If treatment goals are not being achieved, despite medication adjustments, the physician should reevaluate the appropriateness of continued treatment.
d. The physician should monitor patient compliance in medication usage and related treatment plans.

5. Consultation and Referral

a. The physician should be willing to refer the patient as necessary for additional evaluation and treatment in order to achieve treatment objectives.
b. Special attention must be given to those pain patients who are at risk for misusing their medications and those whose living arrangements pose a risk for medication misuse or diversion.
c. The management of pain in patients with a history of substance abuse or with a co-morbid psychiatric disorder requires extra care, monitoring, and documentation, and may require consultation with or referral to an expert in the management of such patients.

6. Medical Records

The physician is **required to keep accurate and complete records** to include, but not be limited to:

a. The complete medical history and a physical examination, including history of drug abuse or dependence, as appropriate;
b. Diagnostic, therapeutic, and laboratory results;
c. Evaluations and consultations;
d. Treatment objectives;
e. Discussion of risks and benefits;
f. Treatments;
g. Medications (including date, type, dosage, and quantity prescribed);
h. Instructions and agreements;
i. Drug testing results; and
j. Periodic reviews.

Records **must remain current, maintained in an accessible manner, readily available for review**, and **must** be in full compliance with State Regulations.

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§9. Apps for Chronic Pain and Other Chronic Health Issues

1. **Ouchie (soon to be known as "Branch")**
   Offers people with chronic pain conditions a wide variety of ways to track and record different aspects of their treatment, all while connecting to a user's personal medical professionals, a medical resource team, and a supportive community. The app also offers evidence-backed tools that encourage functional improvements using techniques like cognitive behavioral therapy (CBT).
   Branch is available on iOS and Android operating systems and is free to users.

2. **ReLeaf**
   With so many different strains, doses, and delivery methods, purchasing medical cannabis can be an overwhelming experience. ReLeaf grew out of the founder Brockelman Franco's experience trying to find relief for his mother, who felt frustrated by the lack of information and intimidated by the stigma around medical marijuana. Empowers users to detail what they're trying, track their own successes with specific treatment methods, and share their results.
   ReLeaf is free and available on iOS and Android.

3. **Pathways Pain Relief**
   Memberships range from one month ($14.99) to the rest of your life ($89.99). Pathways is an app specifically designed for people who have been in chronic pain for over three months. This pain therapy program addresses the physical and mental aspects of chronic pain, with different sections for mindfulness/meditation, physical therapy, as well as a pain and wellbeing tracker and "masterclasses" about different aspects of chronic pain. Pathways also offers meditations specifically designed for pain relief, as well as physiotherapy, yoga, and exercise routines ranging from beginner to expert.
   Pathways is available on iOS and Android, with a web version coming soon.

4. **mySymptoms Food Diary and Symptom Tracker**
   Patients with gastrointestinal issues like IBS, IBD, GERD, celiac, dyspepsia, or food intolerances quickly find out how crucial it is to track their food intake. mySymptoms lets users record food, drink, medication, stress, exercise, environmental factors, energy, sleep quality, bowel movements, and other specific symptoms (including intensity, duration, and other notes), and can export that data in a variety of formats.

mySymptoms is available on iOS and Android.
The full version of the app is $3.99; a “lite” version that is free and ad-supported is also available.

5. **Curable**

Curable is a pain psychology program that uses a biopsychosocial approach to help users better manage their pain. Users of the app are introduced to a virtual pain coach named Clara, who asks a series of questions to get insight into your pain and its causes. She then presents 5-20-minute exercises, like guided meditations and visualizations, and lessons, like creating a pain plan, that aim to help you better manage your health.
The free version of Curable offers 13 free introductory audio lessons, while the paid version, currently $4.99 a month, features a wider variety of exercises building skills in four key areas: pain education, brain training, meditation, and expressive writing.

6. **Bearable**

The health tracker Bearable aims to collect all your medical data in one place. Like all trackers, this app allows the user to record health data. But in addition to general mental and physical health data, Bearable lets you set additional personalized factors like sleep or diet to keep track of. This encrypted data can be searched, used to create graphs and interactive calendars, to recognize trends and stats, and other advanced data insights. It’s also easy to export your data for your own use or to share with your doctor or medical team. Bearable was created by someone with chronic health conditions who found that none of the existing apps offered the kind of wide overall tracking of mood and symptom entries together with other health factors.
Bearable is available on iOS and Android. A free version is available, a monthly premium subscription is $4.49 and an annual subscription is $27.99.

7. **Health Storylines**

Health Storylines has supercharged the idea of a chronic health app that tracks health data and breaks down care plans and interventions into smaller, simple, personalized tools. It can sync with over 300 mobile devices to integrate the health data they provide. Another thing that sets Health Storylines apart is their partnership and integration with patient organizations. Using the Health Storylines platform, organizations like the Allergy and Asthma Network or the Carcinoid Cancer Foundation design and release organization-specific versions of the app that are customized for the condition they focus on.
Health Storylines is free and available on iOS, Android, and as a web app.

8. **Flowly**

The virtual reality app Flowly is an amazing example of how cutting-edge technology can be used to benefit pain patients. Flowly uses interactive

experiences to engage users in biofeedback training, which can teach them to monitor and adjust breathing patterns, focus, and learn how to better regulate their nervous system. The app also keeps track of the user's progress and offers connections to experts and community forums.
You can try a couple of modules for free, but the service is subscription-based. Flowly offers a few different pricing options based on whether you're using an iPhone or a VR headset to experience the app. (Note: the app is only available for iPhone; it does not currently support iPads or Android devices.)

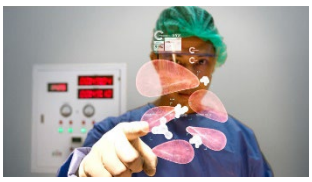
9. **Wave**

Wave was originally designed for cancer treatment, but has been expanded for anyone battling chronic medical conditions. The app is described as "a virtual health advocate that uses Artificial Intelligence to help you track symptoms, medications, and important daily activities to generate your own personal insights that help you take control." It tracks condition-related information like medications and pain scale numbers, as well as more general information like water consumption, sleep, and a step counter. It also uses AI to identify correlations that "help you do more of what helps you feel better, and less of what makes you feel worse," by identifying and highlighting how specific behaviors, activities, and experiences are related to symptom occurrences, moods, and how you feel.
Wave is free. Wave Pro, which is $4.99 a month, also gives users a weekly summary of their data with insights and trends to help take control and get better care.

10. **What's Up? A Mental Health App**

What's Up combines aspects of CBT (Cognitive Behavioural Therapy) and ACT (Acceptance Commitment Therapy) to help users tackle depression, anxiety, anger, and other emotional issues. The app can help point out negative thinking patterns and simple methods to overcome them, like grounding games and breathing exercises. It also features a diary, a habit tracker, and a catastrophe scale to help record problems and keep them in perspective. There are also quotes, useful metaphors, and a forum for users to connect with each other.
What's Up? Is free (supported by donations) and available for iOS and Android.

Manage Your Pain for a Healthier Lifestyle



It can be hard to go through your day with chronic pain. It can affect your mood and performance at work. Some people resolve themselves to chronic pain being something they can't escape from and that is a negative attitude to carry.

A healthy mind and body are the keys to living a fulfilling life. It is important to realize you are not alone and you can get through it. All it takes is a firm resolve to face your pain head-on and conquer it.

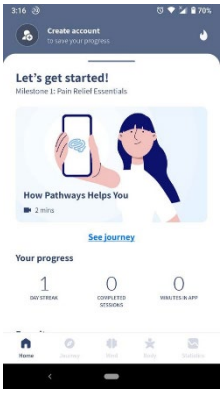
11. **Pain Scale for Healthcare Professionals.** https://www.painscale.com/take-pain-quiz

    - **Email**: help@painscale.com
    - **By mail**: 25155 Rye Canyon Loop, Valencia, CA 91355
    - Corporate Address
    - 300 Boston Scientific Way Marlborough, MA 01752-1234

12. **Pain Check.** https://www.analyticsinsight.net/ai-in-healthcare-ai-in-pain-management-a-new-application/

The following are four Android and iOS apps that help to identify and manage pain, and work with the doctor to treat the symptoms

13. **Pathways Pain Relief**



Pathways Pain Relief is a program designed to help diagnose and offer solutions to chronic pain. It is devised to try and ease chronic pain and even get rid of persistent pain. When pain lasts for longer than three months, your body's pain system can start becoming overactive and overprotective. Pathways' focus is on retraining your brain to reduce the amount of stress and pain.

Pathways' diagnosis helps identify the origin and type of pain, specializing in areas such as back pain, migraines, joint pain, digestive issues, and many more. The program uses a variety of key techniques to help you manage and control your pain including pain science education, breathing visualizations and graded imagery, physical exercise, **meditations**, and stress-reducing exercises.

Pathways' role is a personal pain therapist who will take you on your own journey to understanding why you feel pain, and work to break the pain cycle. You can monitor your performance over time, tracking how your pain develops over time, and focus on the pain relief techniques that work for you. The app gives you the freedom to determine what methods work best for you.

Download: Pathways Pain Relief for **Android** | **iOS** (Free, in-app purchases available)

14. Wave

Wave is a health app for chronic illness patients to track symptoms, medications, sleep, steps, and other activities. You can determine what's impacting your ups and downs, see engaging charts on various fields such as your moods, medications, activities, and sleep, and share all these ongoing reports with your doctors to avoid side effects and improve your care.

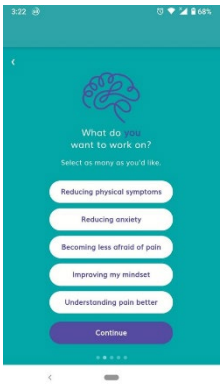
Wave's goal is to provide you with personal insights that enable you to work more effectively with doctors to better control the side effects and symptoms you experience. Wave acts as a virtual advocate for your health and a companion helping you to do everything in your power to feel better.

You can integrate with health devices such a Google Fit to keep an active record of your physical and emotional well-being.

The app uses an AI to generate personal insights based on your own experiences. There are provided in real-time and composed to help you identify how your actions are related to your condition and symptoms, so you can take control of your health while facing chronic illness. You'll discover what's related to your ups and downs and what you can do to take control of your health.

Download: Wave for **Android** | **iOS** (Free trial, subscription required)

15. Curable



Curable is a virtual coach to help you manage and deal with your pain through mental activities. It provides you with guidance and bite-sized audio lessons to teach you, as well as over 100 science-backed exercises for relief. Curable's motto is "Your pain experience is unique, and your recovery program should be, too." It focuses on your needs and health to ensure you are never pushed too far and considers the user's health their priority.

The app is designed by a science advisory team consisting of members in various disciplines. It has been recognized by various industries and is considered the Highest Quality App for Persistent Pain in a large-scale peer-reviewed study evaluating 19 top apps for symptom self-management.

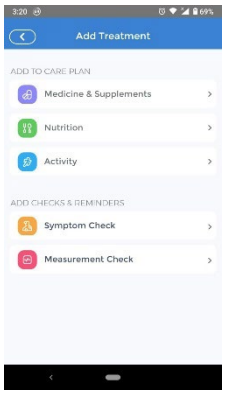
Curable describes itself as a "different approach to your pain." Rather than being medication or physical treatment, its app delves into the brain science of pain to alleviate it.

Curable takes all the information about you and designs a custom program tailored to your symptoms and preferences. The app's goal is to help you realize how much your mental health affects your pain and provide a regime to help you with managing your chronic pain.

Curable has four types of exercises: brain training, education, meditation, and writing. The app monitors your affinity and lessons you are comfortable with and recommends lessons accordingly.

Download: Curable for **Android** | **iOS** (Free trial, subscription required)

16. CareClinic



CareClinic is your daily all-in-one health and wellness app that helps you measure, learn, and improve your health. The app helps you create a care plan to track and manage your symptoms and conditions. It can be used as a pain tracker and symptoms journal. If you are interested in more generalized health trackers, then check out our guide on **the best health journal apps**.

The app allows you to create a treatment and pill organizer to keep track of more than just your medications such as vitamins, supplements, conditions, nutrition, activity, daily vitals, therapies, and automatically discover correlations and triggers. You can take a photo of your prescription and reports to enter information.

CareClinic provides you with a drug and supplements database for references and information. The database also provides nutritional information, allowing you to automatically get calories, micronutrient, and macronutrient information for food and drinks.

Further features include scheduling medication reminders, and a daily check-in diary to record your treatment progress alongside medication reminders. You can record various measurements including PRN, sleep, daily mood, energy levels, pain, and many more. The diary also functions as a symptom diary to log symptom severity.

The app allows you to work with your doctor or caregiver, allowing them to view your care plan and reports. You can correlate summarized reports from your check-ins with your app to see what works and what doesn't alongside your goals.

Download: CareClinic for **Android** | **iOS** (Free trial, subscription required)

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