# ARTICLE
# Meeting Behind the Seen: Synchronous Teaching without Virtual Meeting Fatigue

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Videoconferencing platforms provide opportunities for synchronous teaching and interaction between classmates but they come with disadvantages including video fatigue. Moreover, presenters using videoconferencing programs may feel as if they are lecturing into a void. In an online class on Behavioral Pharmacology, we used Google Meet essentially as a conference call in the background while the class "met" within a Google Doc that everyone could edit. This format permitted both oral and written discussions and gave the students easy access to links posted within the Google Doc directing them to pictures, videos, web pages, and separate Google Meet addresses for small group discussions. For both the instructor and the students, class interaction and engagement were enhanced by the students' ability to add notes and comments to the common Google Doc. We used this technique for a synchronous online class but it could be adapted to hybrid or asynchronous teaching.

*Key words: videoconferencing; meeting fatigue; editable lecture notes; Google Doc*

In March 2020, Transylvania University joined many other institutions in changing its course offerings to be entirely online in response to the pandemic. This resulted in a need to create an online version of Behavioral Pharmacology, a course without labs that is typically taught in our May Term, a four-week intensive session with class held for two hours every day. At the time, the university had Google Suite available, but did not have licenses for Zoom; therefore, our option for holding a synchronous class was Google Meet. I was eager to hold Behavioral Pharmacology as a synchronous course because spontaneous discussions of issues related to drug use are an important component of the course. At the same time, I was mindful of early reports of "virtual meeting fatigue" and had a fair amount of discomfort with being on camera myself. At the time, there was little information on potential causes of or solutions to what is now called Zoom fatigue, but since then psychologists and others have published speculations about the sources of such fatigue (Bailenson, 2021; Bennett et al., 2021; Lee, 2020; McWhirter, 2020). The proposed sources of virtual meeting discomfort include, among other things, extended eye contact with multiple people, the cognitive challenges of following a conversation with audio lag, self-consciousness derived from constantly seeing a view of one's own face, and prolonged immobility (Bailenson, 2021, Bennett et al., 2021).

Although several authors have mentioned distorted nonverbal cues as sources of videoconference fatigue (e.g. Bennett et al., 2021; Lee, 2020), I found a complete lack of nonverbal cues to be particularly problematic during my first two days of teaching, when I was using presentation mode to show the students power point images on brain anatomy and neuron function. This feature of videoconferencing does not seem to have been studied extensively by researchers, but informal sources indicate that other academics transitioning to lecturing by videoconference experienced similar discomfort with lack of interaction with their students (e.g. Nguyen, 2021). In Google Meet, presentation mode left me unable to see the students or to gauge their reactions. Most had muted their microphones as well, so that I had no sense of talking to an engaged audience. Even with pauses in the lecture to allow students to respond, the class sessions lacked the usual verbal and nonverbal give-and-take of a live lecture. I could not conduct a running assessment of the students' comprehension or their ability to follow the pace of information delivery. When I said it was time to take a break, one of my best and most motivated students responded with an enthusiastic "Yes!", which suggested to me that I had asked too much of them. I found myself in a quandary. Behavioral Pharmacology incorporates discussion, but it also requires a certain amount of content delivery to give students background knowledge on which to base their discussions. The first two days of lecture delivery felt unsustainably taxing to both myself and the students because of the lack of easy communication between us, and it was clear that something had to change.

## METHODS

The Behavioral Pharmacology class contained eleven students, all of senior standing (only seniors were permitted to enroll in our May Term 2020). Five of the students had previously taken in-person classes with me, but the remaining six were new to me.

On the third day of class, when we began to explore pharmacokinetics, we started a Google Meet as usual, but I directed the students to a shared Google Doc that all students could edit. This file contained the topic heading written by me, but nothing else, and students were invited to fill out the notes as I lectured. I also entered topic headings as the class went along, as I might do on a whiteboard in an in-person class. The Google Meet functioned as an audio-only conference call running in the background while the

written document remained in the foreground on our screens. I used the conference call to deliver the lecture and incorporated frequent pauses to invite student comments and questions. In this way, students were able to ask questions verbally or to type them in, as well as join discussions either verbally or within the document. The outline of the lecture notes invited students' written participation by leaving space for them to add their own ideas. For example, the pharmacokinetics session began with an outline presenting the four major stages of pharmacokinetics (absorption, distribution, metabolism, and excretion), and, under absorption, listing common routes of drug administration. It became the responsibility of the students to write about the advantages and drawbacks of the different administration methods. Google Meet's audio feature allowed us to discuss some ideas and permitted me to make corrections if necessary.

As the term went on, we started to incorporate additional resources into the shared files. For example, various students and I posted links to news stories, videos, articles containing demographic data about drug use, and songs containing lyrics that described drug effects. I was able to mimic breakout rooms by posting links to new Google Meet sites and assigning students to work in small groups within them. We also took a virtual field trip to the Drug Enforcement Agency's museum of drugs https://www.deamuseum.org. Rather than using screen sharing, which did not always work well because of lag or audio problems, I allotted a certain amount of time for students to watch a video or otherwise explore a site and they were asked to indicate when they had finished by writing their names in the Google Doc we shared.

## RESULTS

Sharing the Google Doc and making it available for all students to edit created a substantial shift in the class dynamic. Although we still used oral discussion, students became increasingly comfortable with putting comments and responses into the document (please see Appendices). They used the shared files to post links to drug-related news items they found interesting, as well as adding pictures that illustrated some of the concepts under discussion. One student enjoyed putting in humorous comments in response to some material and at first quickly erased them, but later started letting them stay when I told her I thought they made good points about the days' topics. I also used the shared notes to post links to documentaries that students could watch after class and encouraged them to post their responses in the notes.

As a teacher, when I saw student responses begin to appear in the document, I no longer felt as if I was talking into an abyss. I also came to appreciate the ease with which we could integrate outside materials into the class's work for the day and I found it easy to identify and correct any factual errors that occurred in the course of note taking. The students also seemed to develop a strong sense of community within the course. They worked cooperatively to flesh out the notes and they held excellent, fruitful discussions in their small Google Meets that they then brought back to share with the class. Eight students contributed to the files on most days, while three contributed more rarely. Although this was not ideal, it shows a similar dynamic to the class participation in our upper-level in-person classes.

To assess student contributions to the lecture files, I viewed the version history of each Google Doc and counted the number of students who contributed along with their names. The lowest number of contributors in a day was 7 and the highest number was 11, with a mean of 9.33. I also counted the total number of lectures to which each student contributed. The number of days each student contributed was highly correlated with the final grade in the course ($r = .899$, $df = 9$, $p < .001$) even though I did not include contributions to the notes within my grading schema.

In Appendix 1, I have provided examples of notes or other resources I used to develop the shared Google Docs along with anonymized versions of the shared Google Docs. Appendix 1 shows the filled-out lecture notes for the Pharmacokinetics session, the first session in which I used the Google Docs and audio conference technique. Students filled out the notes in response to comments I made in my lecture and to ideas they developed as they talked among themselves. As the lecture progressed, I added images from Power Point slides available from our textbook publisher and I added the names of drugs illustrating specific pharmacokinetic characteristics. A view of the document's history indicated that 10 of the 11 students contributed to editing the file. This lecture continued into a different class day during which 7 of the 11 students edited the file.

Appendix 2 shows the shared Google Doc from a class session six days into the new format, when we were covering drugs for bipolar disorder. Appendix 2a is what the file looked like after I had prepared it for class but before the class began. Appendix 2b is what it looked like at the end of the class period. This file shows how I incorporated an opportunity for small group work into the document. Google Meet did not have a breakout room function, but I was able to generate and embed separate links to other Google Meet sites where group work could take place.

On the second-to-last day of lecture, three and a half weeks into May Term, we had a class session on the opiate and opioid drugs. Appendix 3 is an anonymized copy of the shared document from the May Term 2020 online class. I have put a few annotations in this example in order to show the level of class engagement reflected in some of the written conversations within this document. This document also shows that activities such as joint visits to other web sites can be embedded into the class session and it includes a link to a news item that a student who was doing a drug profile paper on oxycodone wanted to share and discuss with the class.

Assessment in this class included two take-home exams that asked students to apply knowledge obtained in the course to answering some complex questions related to medical or drug policy issues. Students were permitted to use the shared notes and the textbook to take the exams and were expected to cite these sources in their answers to the questions. Although the students varied in their performance, they generally did well at demonstrating

knowledge of pharmacological principles and applying them to novel questions. Grades on the first exam ranged from 58 to 99, with a mean of 88.09. On the second exam grades ranged from 71 to 100, with a mean of 91.09. It was notable that the students who made the fewest contributions to the shared note taking were least likely to produce sophisticated answers to the questions on the exams, with Pearson correlation coefficients above 0.8 between total days of contributing to lectures and scores on Exam 1 (r = .889) and Exam 2 (r = .842).

The other major means of assessment in the course was a drug profile paper in which each student wrote and presented about the pharmacology, legal status, and social impact of a specific psychoactive drug, in addition to reviewing some recent research about that drug. This was the only assignment that permitted direct comparison with performance of students in prior years. The students' performance on this assignment was much like performance in other years (e.g., 2018 full-semester, in-person class with 23 students, M = 86.70, SD (pop) = 10.344; 2019 May Term in-person class with 9 students, M = 90.00, SD (pop) = 5.416; 2020 May Term online class with 11 students, M = 90.18, SD (pop) = 11.621; 2021 full-semester online class with 19 students, M = 88.42, SD (pop) = 7.576). These results indicated that the practice of meeting within the Google Doc and using videoconferencing only as an audio tool did not generally inhibit their learning.

## DISCUSSION

Since the development of the Google Docs app, instructors at the K-12 through university levels have described its usefulness for supporting collaborative student projects, allowing instructors to give feedback to students easily, facilitating submission of course assignments, and integrating with assignments in learning management systems (Li, 2019; Olesen, 2020). Here I describe a use of the app to facilitate synchronous online teaching and learning and to take advantage of videoconferencing software while reducing the features of that software associated with virtual meeting fatigue.

This report describes an online classroom setup in which the class took place "within" a shared Google Doc that everyone in the class could edit, while an audio-only Google Meet ran in the background to facilitate lectures and oral discussion. The shared document file contained an outline of the lecture that the students filled out and offered spaces to insert written comments about the material and post outcomes of small group discussions. The class was unusual in that it contained a small number of students, all seniors. All of us were grappling with developing new learning strategies in the face of an abrupt shift to fully online teaching. Student engagement with this form of classwork was substantial, with all students contributing at least occasionally to the shared notes. The course assessments indicated that the level of learning in these students was equivalent to that shown in live classes.

In the summer of 2020, our institution purchased Zoom licenses and online teaching became a regular feature of our academic environment. Although I switched to Zoom, I maintained the use of the shared lecture note Google Docs for my classes and I continued to have some class sessions in which the students and I spend most of the session working within the document. There are several reasons for doing so:

(1) The lecture notes orient the students to the structure of the class and assist them in taking their own notes. A first-year student who started her college career in Fall 2020, when most of our classes were online, told me that she was grateful to have the outline because it helped her understand how to take notes at the college level. More experienced students have expressed a strong, even unanimous, preference for having the notes available and, in the majority of cases, for working within a document incorporating some pictures over looking at a slide presentation and hearing a lecture on it. They expressed this preference in informal discussions I conducted throughout the semester during which I listened to their suggestions for how to make online learning more comfortable for them. The shared notes have been useful for students needing note-taking accommodation in particular, but they seem to be appreciated by students as a whole.

(2) The shared Google Docs provide students with a long-term record of links to videos or other resources pertinent to the day's topic. Video links posted in Zoom chats tend to be more ephemeral. Moreover, having had several screen-sharing experiences involving videos that did not work as smoothly as planned, I learned that having students follow their own link to a video can work more efficiently within the class.

(3) The shared document makes a more easily used "whiteboard" than the whiteboard function within Zoom. Working within the document, I can spontaneously write vocabulary words or other information without needing to transfer to a different shared screen or type within the chat function. It is also a readily accessed space for student collaboration. I used it in my Statistics class to have students work together on problems. In my Sensation and Perception class, students used the document to post data from activities they completed, and the patterns in the data then became topics of discussions and lab reports. (Students were informed that they did not have to contribute their data if they preferred not to.)

In all, the regular incorporation of the shared Google Doc into the online class has added flexibility to my online teaching and created a workspace that students can take advantage of in a variety of ways. They appeared comfortable within the collaborative document and I noticed that in my Fall 2020 synchronous classes they tended to join the shared document several minutes before they joined the Zoom meeting. Although the use of Google Docs is not as central to the course as it was in my early online Behavioral Pharmacology class, it continues to play an important role in the teaching and it has served diverse student needs.

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# APPENDIX 1

## Completed Google Doc at the End of the Pharmacokinetics Class Sessions

**Disclaimer: In all Appendices, the notes are presented in rough form, as they were received from the students. Some punctuation was added to enhance their clarity.**

**Pharmacokinetics Notes <-- This document opened on the class day just with the heading, no other material**

**Absorption**

- Definition: Moving the drug from the site of the administration to the bloodstream
- Enteral routes- routes of absorption/ administration that involve the GI tract ex: oral, rectal
- Parenteral routes- routes of absorption/ administration that don't involve the GI tract Ex; transmembrane, transdermal, pulmonary, injection
- Lipid soluble - I typed this in as a characteristic drugs need in order to be absorbed, rather than a type of administration. It applies to all modes of administration as a relevant characteristic, except that drugs that are not lipid soluble can be injected intravenously potentially. - MU
- Oral -
    - Advantages:
        - Relatively easy- requires no needles, shots, etc. / accessible
        - Not as fast as direct injection to the bloodstream i.e., IV injection
        - Pain avoidance
    - Disadvantages
        - Stomach distress/ vomiting
        - Acid in the stomach can destroy some of the drug
        - Not as fast as direct injection to the bloodstream i.e. IV injection
        - The rate at which a tablet dissolves and its chemistry limit the rate of absorption.
        - Drugs must be soluble in fat.

- Transmembrane - mucus membranes, skin
    - Mucus membranes (nose, cheek: Flonase, Cocaine)
        - Advantages
            - Direct access to the bloodstream
            - Avoids degradation of stomach fluids
            - Enters system quickly
            - Minimizes pain especially for children
            - Quick and easy administration
        - Disadvantages
            - Membranes are fragile/ these surfaces are not impermeable barriers (as opposed to the skin) :( hole in nose
            - Might cause inflammation at mucosae (which is bad… the body's reaction would often be considered a cause of disease rather than a cure)

- Transdermal (through the skin: nicotine patches)
    - Advantages
        - Minimizes potential side effects due to fast release
        - Slow, continuous absorption of the drug over hours or even days.
        - Easy to apply (non-invasive)
        - Reduce dose frequency

    - Disadvantages
        - Allergic reaction
        - Rate of absorption is slow so might not be a good method if you want fast absorption
        - Limited to substances that are highly lipid soluble because skin presents a number of barriers to absorption. However, the solvent DMSO can allow almost any drug to be absorbed through the skin
- By injection
    - Intravenous (Directly into a vein)
        - Advantages
            - Great for emergency use
            - Direct access to circulatory system
            - Fast absorption rate
            - Can be diluted
            - Instant drug action (or termination)
        - Disadvantages
            - Allergic reactions can occur
            - Pain factor with injection
            - Instant drug action (or termination)
            - Can't use oily substances
            - You have to be super careful not to inject air, or you might clot the blood
            - One of the most dangerous of all routes of administration because of the rapid onset of action: Too-rapid injection can be catastrophic, producing life-threatening reactions.
    - Intramuscular (Directly into a muscle)
        - Advantages
            - Good for irritating substances
            - Can use oily substances
            - Sustained effect
        - Disadvantages
            - Precluded during anticoagulant medication.
            - May interfere with interpretation of certain diagnostic tests.
            - Pain factor with injection site - sore muscle
            - Incomplete absorption
            - Slightly trickier than other types of injections
    - Subcutaneous (Just under the skin)
        - Advantages:
            - Allows for slow absorption over a period of time
            - Low dosage of the drug may last longer
        - Disadvantages:
            - Not suitable for large volumes
            - Possible pain or necrosis from the irritating substances
    - Implantation - bolus in muscle or under skin
        - Advantages:
            - Allows for absorption over a period of time with an implant - i.e., insulin administration via implant
        - Disadvantages:
            - Initial implantation/removal is painful
- Pulmonary (through lungs)
    - Advantages
        - Rapid absorption within seconds because of large surface area of lungs
        - Goes directly from the lungs to heart and then to the brain
    - Disadvantages

        - Due to the rapid onset, drugs used this way can promote compulsive use
        - Can potentially cause smoke damage to the lungs (Ex. smoking cigarettes or joints)
        - Even if vapor is inhaled instead of smoke, potential for lung damage exists
        - Effects can be very intense (positive/ negative)

**Distribution**

- Circulation of drug throughout the body, has to happen for drug to be carried to brain
- Tissue reservoirs: fat - THC, bone - heavy metals, proteins in blood plasma (e.g., albumin) - potential source of drug interactions. Drugs bound to plasma proteins are unavailable to tissue. Dosing has to compensate for that. But if another drug is administered that displaces the first one from the plasma protein, then suddenly too much of the first one might become available → overdose.
- Tissue barriers: e.g., blood-brain barrier - tight capillary walls, end feet of glial cells
    - Drugs must be lipid soluble to pass through barrier and reach the brain. Thus, there are a lot of drugs that we can't use to treat brain diseases/infections, but also keeps a lot of unwanted things out of the brain.
    - Imodium - anti-diarrhea drug (opiate that is not addictive because it can't cross the blood-brain barrier)

**Metabolism**

- Metabolic breakdown of drug (chemical alteration)
    - Via specialized enzymes - Cytochrome P450 family
- Enzyme induction- Increase enzyme production, a means of drug tolerance and cross tolerance (Can be tolerant to one drug and that automatically makes you tolerant to a different drug); caused by specific exposure to that drug. One of the aspects of drug interaction.
- Competition between drugs for access to enzymes, potential source of drug interactions
    - Almost the opposite of the enzyme induction
    - Example: SSRI and anxiety as side effect; combining SSRI and Caffeine- SSRI will compete for the enzyme that breaks down caffeine- high caffeine levels → interpreted as anxiety
    - One drug might beat out another drug for enzyme access which can cause an overdose
- Consequences of metabolism
    - Active substance → Inactive substance
        - happens pretty regularly
    - Active substance → Different Active substance
        - (fluoxetine → norfluoxetine → inactive metabolite)
        - greatly changes the amount of time there's a psychoactive response,
        - "Two drugs in one"
    - Active substance → Toxin
        - alcohol → acetaldehyde (toxic exposure aka hangover))
        - Tylenol (damages liver)
    - Inactive substance (prodrug - what you take to get a drug) → Active substance
        - Vyvanse → amphetamine (Vyvanse must be metabolized to have the effect, can't be snorted, etc.)
        - Heroin → Morphine (heroin only has its effects when converted to morphine)

**Excretion**

- Urine
    - Urine is the most common excretion method. (Kidney) Why we have urine tests for drug tests!
    - Municipal water systems have drug metabolizing because you can't filter out drugs. Ecological effects: hormones peed into the water system because of increased birth control use→ aquatic life getting genderbent and abnormal development
    - ARE WE DRINKING BIRTH CONTROL WATER? SHOCKING!
- Bile
    - Second most common type

    - Accumulates and goes out through feces
- Breath
    - Drug must be something that can be vaporized
    - Inhaled and excreted
    - E.g., alcohol, anesthetics
- Sweat, Blood, and Tears
    - Minor ways but could potentially be detected in tears
- Saliva - cotinine (nicotine metabolite) Fun fact 1: Cotinine is anagram of the drug it's made from
- Hair and Nails
    - Very slow growing
    - Can test by hair sampling. Drug metabolite enters hair at root, but is carried along as the hair grows out. As long as the person doesn't get a haircut, the metabolite can be detected.
    - Potential use in forensics
    - E.g., exposure to arsenic can be detected this way.
- "Operation Golden Flow" Fun act 2!
    - Military operation: army's drug-testing program

**Important Graphs**

**Graph 1:** Here I inserted a graph from the textbook publisher illustrating drug concentration over successive half-lives and demonstrating that a steady-state concentration can be achieved by administering a dose of the drug once every half-life. Because publication in JUNE is not included under fair use, I have removed this graph and the one described below.

- Graph 1: drug half-life (how long it takes a drug to reach half of its concentration in the body).
    - Time 0: 100 mg, half-life 1 hour→ after 1 hr: 50 mg, after 2 hr: 25, after 3 hr: 12.5 mg, etc.
    - If you keep dividing, all of the drug will be gone within 6 hours.
    - Once you reach 6 half-lives of providing the dose every one half-life, the drug will be in steady state. Don't want fluctuations, want a steady state to be reached.

**Graph 2:** Here I inserted a graph from the textbook publisher illustrating how drug concentration changes over time and demonstrating that the time window of a therapeutic effect is shorter than the time window of the drug's presence in the body.

- Graph 2: Therapeutic window (a well-defined range of blood levels associated with optimal clinical response)
    - Levels either below or above the range is associated with a poor response.
    - When you administer a drug, there will be a period of time before it has an effect. For ex., if you take an aspirin for a headache, it doesn't immediately treat the headache. With time, it will get the desired effect…
    - Eventually, the drug will be metabolized/ go below the desired level. So, aspirin for example, will give you relief for some time but then goes to a low enough level where it is no longer doing that anymore. (This is when you could potentially take another aspirin).

****Important aspect of the image: even when the drug is not having an effect, it is still present in the person's system (just at a low level). This can be okay in terms of aspirin.

        - When would this be a concern? other drugs (like sleeping pills ZZZZ) could be problematic because you might be accumulating it on top of another existing sleeping pill that is going to make your dose too high.
    - We want different lengths of time for different drugs (e.g., anesthetic - we want it to enter quickly and leave quickly - very short half life vs. antiseizure drugs which we want to stabilize a person so they can potentially take the drug only once a day)
    - **A:** Shape is an inverted U: After the therapeutic effect reaches a plateau, an increase in dose does not produce further improvement, but may actually decrease the drug's effectiveness

# APPENDIX 2

## A. My lecture outline for the drugs for bipolar disorder as it existed just before the start of class. I have removed the names of students in compliance with FERPA guidelines.

**Drugs for Bipolar Disorder**

One man's experience with bipolar disorder and treatment: https://www.youtube.com/watch?v=LuFbEKQME4A:

Convene here for discussion by 1:15: https://meet.google.com/dht-egoz-zig

Question: What kind of therapy did the man in this video receive? How can you tell?

**Symptoms of Bipolar Disorder**

Bipolar I - severe mania, with or without depression

Bipolar II - hypomania, presence of depression

Cyclothymia - less severe, but long-lasting

Often the person will present with depression and be misdiagnosed, potentially treated with drugs that make the situation worse.

Problems associated with mania:

Problems associated with depression:

The big challenge: controlling manic episodes *and* controlling depressive episodes *and* maintaining a stable mood, preventing a return to the manic or depressive state.

**Treatments**

Like schizophrenia, bipolar disorder will need attention throughout someone's life. It was and is a reason for short-term or long-term hospitalization.

Support for the person should include therapy. Why?

**Lithium**

We will have a presentation on this, but just to give some basic facts, this was and continues to be one of the most effective drugs for all stages of bipolar disorder. Not everyone responds, but around 60-70% do.

Benefits:

Problems:

The issue of "noncompliance" - patient does not take drug as directed.

**Antiepileptics/Mood Stabilizers**

- **Those believed to enhance GABA function**
  - Valproic acid
  - Gabapentin

- **Those that alter firing by acting on voltage-gated sodium channels**
  - Lamotrigine
  - Carbamazepine
  - Oxcarbazepine
  - Topiramate (blocks potassium channels too)

In terms of their clinical effectiveness, rated on p. 535, is there any pattern that you can see?

**Second Generation Antipsychotics**

Historical note and pop quiz: the FGA haloperidol used to be administered frequently to control mania and it worked pretty well. But what would be a problem with using an FGA? Why was there a switch to SGAs for control of bipolar disorder?

Based on the information provided, what would you as a clinician potentially use to:

1. Bring a person out of an acute manic state?
2. Bring a person out of an acute depressive state?
3. Maintain stability (euthymia) in a person not currently experiencing mania or depression?
4. Address the needs of someone who experiences rapid cycling?

Out of the SGAs, which would you pick to assist in controlling bipolar disorder, and why?

**Antidepressants in Bipolar Disorder**

Evidence for and against using them

**The Role of Therapy**

**Prenatal Effects of Drugs Used to Treat Bipolar and Other Disorders Covered in this Section**

**Relative risks:** Remember that risks must be balanced against the risks of leaving the disorder untreated. Also remember that miscarriages, low birth weight, and birth defects can occur when no drugs or underlying disorders are present.

**Group 1 (Students A, B, and C) :** Relative risk of birth defects from antipsychotic drugs

Meet here: https://meet.google.com/lookup/ciz2n2zzkk

**Group 2 (Students D, E, F, and G)** : Relative risk of birth defects from antiepileptic drugs

Meet here: https://meet.google.com/lookup/dlrav4qk3p

**Group 3 (Students H, I, J, and K)** : Relative risk of birth defects from antidepressant drugs

Meet here: https://meet.google.com/lookup/bniaglvwk4

Pregnancy criminalization, eugenic concepts

Reconvene here for discussion: https://meet.google.com/dht-egoz-zig

**B. Lecture Notes as They Existed at the End of Class. Annotations in Red Font were Added for This Paper.**

**Drugs for Bipolar Disorder**

One man's experience with bipolar disorder and treatment: https://www.youtube.com/watch?v=LuFbEKQME4A:
Example of a link embedded in the shared document that students were to visit and watch independently.

Convene here for a discussion by 1:15: https://meet.google.com/dht-egoz-zig

Question: What kind of therapy did the man in this video receive? How can you tell?

- Second therapist took a CBT approach – elements: made him do activities, goal setting, → feeling of accomplishment, that his diagnosis was manageable and needed to be managed
- Therapy+ medication is important for recovery and management

**Symptoms of Bipolar Disorder**
**Therapy is crucial to recovery, not just medication**

- Bipolar I – severe mania, with or without depression
    - Manic episode: an elevated expansive mood or irritability, excess
    - Severe mania can be accompanied by psychosis
    - Genetic overlap with schizophrenia
    - Delusions and hallucinations with mania
- Bipolar II – hypomania, presence of depression
    - Mania is less severe (hypomania). Maybe a desirable state for the person, but is accompanied by depression.
    - One challenge: when getting treated, the drugs will take away their pleasure as well as their depression. Takes away their high.
    - Sometimes people with bipolar II may present at a physician's office depression and there is a misdiagnosis of bipolar II as depression.
        - Prescribe antidepressants when misdiagnosed as depression but this could result in a manic flip so that the patient's mania becomes worse because of the antidepressant.
- Cyclothymia – less severe, but long-lasting (at least 2 years)
    - Has to impair the person's daily function

Often the person will present with depression and be misdiagnosed, potentially treated with drugs that make the situation worse.

- Problems associated with mania:
    - Grandiosity which can lead to financial problems or personal risk
    - Risk of taking sedative-hypnotic drug to calm mania
    - Manic episodes can be displayed through lack of sleep, impaired judgement.
    - Reduced need for sleep
    - Excessive talking
    - Risk of substance use disorder, especially with lithium
    - High distractibility- can't filter out extraneous stimuli
    - Flight of ideas- difficult to complete one thought before starting another
    - Along with risks, people can get into trouble sexually – sexual deviancy – legally or personally
- Problems associated with depression:

    - Lack of desire/ motivation to do things: impairs job, school performance, and relationships.
    - Alcohol abuse or other substance abuse
    - Suicide: potential during the manic phase
    - Loss of job due to depression
    - May be especially vulnerable to putting yourself down following a manic episode.
    - Substance abuse risk
- Demographics of Bipolar
    - 1% of population
    - Equally male and female, unlike unipolar depression (found more frequently in females)

**The big challenge:** controlling manic episodes *and* controlling depressive episodes *and* maintaining a stable mood, preventing a return to the manic or depressive state

**Treatments**

- Like schizophrenia, bipolar disorder will need attention throughout someone's life. It was and is a reason for short-term or long-term hospitalization.
    - Life-long treatment, find drug treatments that work and that the person can tolerate
- Support for the person should include therapy. Why?
    - Need help from someone to show them the way and give goals and keep them going. Like a way to provide direction (from short clip).
    - With Bipolar II the person might miss the manic episodes and forgo medication in order to get them back – must remind them of medication benefits (medication maintenance)
    - Remind the person of adaptive vs. maladaptive behaviors
    - Someone with manic episodes are difficult to live with and may cause marriage/family relationships to fall apart – therapy can help them identify the issues and help maintain these relationships

**Lithium (stacking the guinea pigs)**

We will have a presentation on this, but just to give some basic facts, this was and continues to be one of the most effective drugs for all stages of bipolar disorder. Not everyone responds, but around 60-70% do. One of the students in class was writing a drug profile paper on lithium and would make a presentation on it at the end of the term.

Metallic element that occurs in nature as a mineral salt and is an effective treatment for bipolar disorders. Approved in 1970.

- Benefits: Very effective
    - 60-70% (compared to other drugs types this is much better)
    - Unusual in that it affects all phases of bipolar
    - The gold standard of drugs for bipolar disorder
- Problems:
    - Narrow therapeutic window – not enough = not effective, too much = overdose
    - Can cause kidney damage
    - Can cause problems in thyroid functioning
    - If person is suicidal (depressive episode), Lithium is easy to overdose on (narrow therapeutic window)
    - Although more than 60% of patients with mania improve on these medications, the risk of relapse is 28 times higher if patients stop taking a mood stabilizer.
        - Suggesting the drugs are prophylactic

The issue of "noncompliance" – patient doesn't take the drug as directed.

- Things to consider:
    - They just generally don't like how the drug makes them feel (adverse effects) – personal risk/benefit analysis of medication
        - Consider effects of treating adverse effects/ "misdiagnosing"
    - Miss manic episodes (Bipolar II)
    - Movement disorders
    - Bipolar II issue of loss of mood fluctuations due to medication

**Antiepileptics/Mood Stabilizers**

- **Those believed to enhance GABA function**
    - Valproic acid: substantially effective in acute mania/ mixed, effective in acute bipolar depression, and possibly effective as a mood stabilizer prophylaxis.
    - Gabapentin: not effective in acute mania/ mixed, acute bipolar depression or as a mood stabilizer prophylaxis

- **Those that alter firing by acting on voltage-gated sodium channels**
    - Lamotrigine: Not effective in acute mania/mixed. Substantially effective in acute bipolar depression and as a mood stabilizer prophylaxis.
    - Carbamazepine: substantially effective in acute mania/ mixed, effective in acute bipolar depression, and possibly effective as a mood stabilizer prophylaxis (Same as Valproic acid)
    - Oxcarbazepine: "essentially carbamazepine with an O2 molecule" > safer! Can be used to treat epilepsy, bipolar disorder, and acute mania.
    - Topiramate (blocks potassium channels too): Not effective in acute mania/mixed, acute bipolar depression or as a mood stabilizer prophylaxis. Possibly effective as a mood stabilizer prophylaxis.

In terms of their clinical effectiveness, rated on p. 535, is there any pattern that you can see?

**Conclusions:**

- A large majority treat acute mania
- No consistent pattern which makes treatment from person to person very difficult, no prediction of what a drug might be good at or not good at

**Second Generation Antipsychotics**

Historical note and pop quiz: the FGA haloperidol used to be administered frequently to control mania and it worked pretty well. But what would be a problem with using an FGA?

- First generation antipsychotics cause movement disorders, so medical professionals are discouraged against using first generation antipsychotics to treat bipolar disorder. Using haloperidol could cause people to not detect the nausea caused by lithium overdose (haloperidol has anti-nausea effect). So people would miss an early sign of lithium toxicity and might experience kidney damage. Students' answers, with guiding by me about effects of haloperidol on experience of nausea.

Based on the information provided, what would you as a clinician potentially use to:

1. Bring a person out of an acute manic state?
    - I would choose Risperidone because it would not only treat the mania but stabilize the mood
2. Bring a person out of an acute depressive state?

- I would choose Lamotrigine because it will treat the depression and stabilize the mood

3. Maintain stability (euthymia) in a person not currently experiencing mania or depression?
    - Risperidone because it helps prevent remission and also avoids inducing depression. This would be used as a monotherapy
4. Address the needs of someone who experiences rapid cycling?
    - Cycling between mania, depression, and normal states varies person to person, but the faster a person experiences the different states – the more rapid cycling – the more severe the psychopathology. This means that finding the proper medication along with supportive psychotherapy are imperative.
    - I would choose Quetiapine because it will treat both mania, depression, and stabilize the mood, and is highly effective in the treatment in each of these categories.

Out of the SGAs, which would you pick to assist in controlling bipolar disorder, and why?

Prodromal therapy – treat the disorder before it emerges in full

**Antidepressants in Bipolar Disorder**

- Antidepressants by themselves are a big NO, they can increase the manic episodes, when used in combination use them reluctantly
- Evidence for and against using them – olanzapine (Zyprexa) and fluoxetine (Prozac) affective antidepressant and antimanic mix (Symbyax)

**The Role of Therapy**

**Prenatal Effects of Drugs Used to Treat Bipolar and Other Disorders Covered in this Section**

**Relative risks:** Remember that risks must be balanced against the risks of leaving the disorder untreated. Also remember that miscarriages, low birth weight, and birth defects can occur when no drugs or underlying disorders are present.

Students were directed to separate Google Meet spaces for their work in small groups.

**Group 1 (Students A, B, and C) :** Relative risk of birth defects from antipsychotic drugs

Meet here: https://meet.google.com/lookup/ciz2n2zzkk

- There is no increased risk for miscarriage with antipsychotics. More research needs to be done for this to be conclusive.
- There is no increased risk for birth defects or stillbirths with antipsychotics. More research needs to be done for this to be conclusive.
- There is a potential risk of lower or higher birth weights.
- Evidence shows that women on antipsychotics are 2x more likely to get gestational diabetes; however, evidence also suggests that women who suffer from psychotic illnesses and do not take medication have an increased chance of developing gestational diabetes.
- Resperidone is the most studied antipsychotic (based on NIH and Rcpsych).
    - There have been studies that show birth defects, but “more research is needed’.
- Antipsychotics can contribute to birth defects especially in the third trimester, which is when many important organs and structures develop.

- According to the FDA, there is a potential risk of abnormal muscle movements and withdrawal in newborns whose mother was taking antipsychotics during pregnancy. Symptoms include: agitation, hypertonia (too much muscle tone resulting in stiffness), hypotonia (too little muscle tone resulting in floppiness), tremors, drowsiness, and more.
- Currently, the most commonly used antipsychotics during pregnancy are olanzapine, risperidone, and quetiapine; there is no specific evidence that they cause fetal malformations.
- While many antipsychotics are found in breast milk and shown to penetrate the fetus, research cannot conclude that antipsychotics do cause birth defects.
    - There were incidences where muscle development was irregular in infants.
    - It seems that the first trimester is when birth defects are most likely to occur/be caused by antipsychotics.
- Much of the research available was extensive in analysis of pregnancy and placenta/fetus observations. However, many studies stated that the effects of these antipsychotics were unknown during lactation
    - Some traces of antipsychotics were found in breastmilk, but the research indicated that it was not enough to cause any risks or changes to the child.
- The current research appears to be somewhat biased, and may not include enough diversity in participants (most were white and of higher social class).
    - But couldn't this reflect on the individuals who are able to afford antipsychotics?
        - Maybe the research is analyzing the population most reflective of the current demographics of antipsychotic users.

**Group 2 (Students D, E, F, and G)** : Relative risk of birth defects from antiepileptic drugs

- Women with epilepsy and seizures have higher risk of perinatal complications, such as premature delivery, hemorrhage, and stillbirth; however, majority of women with epilepsy have normal, healthy babies
- A study done in England found that 4% of births to women with epilepsy had a major congenital malformation:
    - Drug regimens that featured multiple drugs caused higher risks.
    - Regimens that contained Valproate had significantly more birth defects then regimens that did not
    - For single drug regimens, carbamazepine showed the lowest risk of birth defects.
    - Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2077578/
    - This suggests that antiepileptic drugs do have a small risk of causing birth defects. During pregnancy and before, mothers with epilepsy should try to limit or change their drug regimen to include less drugs and also try to switch to the drugs that have been shown to present less risk.
- FACS (Fetal Anticonvulsant Syndrome):
    - Delayed walking and talking, poor speech, problems in memory, lower intelligence in behavior – sodium valproate seems to be a high risk factor.
- In a study of 203 pregnant women who were exposed to topiramate during the first 12 weeks of pregnancy, 178 resulted in a live birth, of which 31 had some form of birth defect. Sixteen of these live births were major congenital malformations.
    - 3/16 came from exposure to topiramate.
    - 13/16 came from exposure to topiramate taken in combination with other antiepileptic medication.
    - This study found that there is a greater risk of malformation when there is additional exposure to another antiepileptic drug along with topiramate.
    - Source: https://www.nhs.uk/news/pregnancy-and-child/antiepileptic-drugs-and-birth-defects/

- CDC study on antiepileptic medication use during pregnancy:
    - Concluded that women who need to use this medication, but are also pregnant, should talk with their doctors about lowering their dose, or switching to a lower risk medication during their pregnancy
    - About 40 infants with spina bifida and 35 infants with cleft palates could be traced back to mother's use of valproic acid during pregnancy
    - Similarly, 5 infants with a cleft palate and 5 infants with spina bifida could be traced back to the mother's use of carbamazepine
    - Valproic acid poses the most risk to a fetus in terms of developing birth defects
    - Source:
        - https://www.cdc.gov/ncbddd/birthdefects/features/birthdefects-meds-preg-spinabifida.html

Meet here: https://meet.google.com/lookup/dlrav4qk3p

**Group 3 (Students H, I, J, and K)** : Relative risk of birth defects from antidepressant drugs

- Research has found that prenatal antidepressant use was associated with increased anxiety symptoms in children by the age of 3.
    - In this study, however, the prenatal antidepressant did not present emotional reactivity, somatic complaints, sleep problems, attention problems or aggression in the child at 3 years.
    - Another major finding was that the mothers' depression was independently related with child behavior problems (https://doi.org/10.1093/ije/dyv030).
- Neonatal withdrawal symptoms reported in a few cases involving clomipramine, desipramine, and imipramine (antidepressants, tricyclic)
- Risk of postnatal behavioral abnormalities in the child exposed to medication in utero
- Risk of perinatal syndromes - within several weeks immediately before/after birth
- Neonatal toxicity in child if the mother continues medications while breast-feeding
- Mothers that took Zoloft (sertraline) had double the risk of having babies with a heart defect, while those who took Paxil (paroxetine) had more than three times the risk

Meet here: https://meet.google.com/lookup/bniaglvwk4

Reconvene here for discussion: https://meet.google.com/dht-egoz-zig

# APPENDIX 3

**Sample of a Class Document from close to the end of May Term. Annotations in Red Font were Added for This Paper.**

**Opiates and Opioids**

Meet here: https://meet.google.com/lookup/fehi355gib

Let's begin by taking a virtual field trip to the DEA Museum. We will start with opium history and click over to production and distribution: https://www.deamuseum.org/ccp/opium/history.html.
Students went to the DEA Museum site on their own rather than through screen sharing, but I directed them through their visit by providing audio instructions as we view the site.

- A Little US Opiate/Users in the US
    - DEA Museum did not point out that Chinese workers who built the railroads were paid in opium
        - Cheap for the railroad companies
        - Disastrous for the workers
    - Other users in the 1800s
        - Soldiers during and after the Civil War
        - Helped them deal with the pain of their injuries
        - A high rate of addiction - "The soldiers' disease"
        - Amplified by the development and use of the hypodermic needle
    - Housewives, farm wives
        - The Mother's Little Helper of the 19th Century
        - "Health tonics" containing codeine or morphine did not indicate that they contained it
            - You got addicted lol
        - Delivered by mail order businesses like Sears Roebuck (ancestor of Sears department stores)
        - Wells Fargo wagon would deliver
        - But what if they were late, or there was a blizzard?
    - In Germany: Invention of the "nonaddictive" painkiller Heroin (oops)
        - Spoiler alert: it's really addictive
        - Soon came to the US
        - Prohibited in the early 1900s, but, you know by now, the 1920s were a wild time, so of course they used it
        - Heroin closely associated with jazz
        - Federal Medical Center in Lexington was at one time a "Narcotic Farm" to house and rehabilitate heroin addicts
        - "The Narcotic Farm", an excellent documentary that relates to many themes we have covered: https://vimeo.com/97168417

    - Vietnam War brought heroin back into greater rates of use
    - Changes in medical ideas about the treatment of pain
        - The belief that people using an opioid for pain relief would not get addicted
            - A single f-in letter!!!!!!!!!!!! <-- This is a student's reaction to hearing that the belief that oxycodone was not addicting when used to treat pain was based on a single letter that a

clinician wrote to a medical journal. A physician who worked in a hospital happened to notice that patients who were prescribed opioids did not seem to get addicted.

- The current situation
  - KY highest rates of death by cancer; opiates prescribed for cancer treatment
  - Coal mining/ physically demanding; physical trauma from workplace environment→ poor area with not much rehabilitation/recovery centers
  - https://www.washingtonpost.com/investigations/opioid-death-rates-soared-in-communities-where-pain-pills-flowed/2019/07/17/f3595da4-a8a4-11e9-a3a6-ab670962db05_story.html. A student wanted to share this story with the class to hear others' reaction to the situation.
  - No one starts out as an addict!

- Opiates
  - Characterized: extracted from opium (poppies natural substance)
  - Codeine
  - Morphine
    - Only pure opiates
  - Both derived from the juice of the opium poppy
- Opioids
  - Semisynthetic – heroin, a modification of morphine
  - Synthetic – ex. Fentanyl (made by people)
  - Our very own, we make these in our bodies -- endorphins, enkephalins, dynorphin
    - We have receptors for these and these receptors are what the drugs target.
- Opioid receptor subtypes (targets of the drugs)
  - Mu (MOP) – euphoria, pain relief, stress relief, respiratory depression, major addictive pain medications are agonists here
    - Examples of natural endorphin release: runner's high, a good cry, a child being comforted by mother when upset
    - In high amounts you can get pain and stress relief
    - Respiratory depression: these effects may sound great but there is also the risk of respiratory depression. Can't get rid of this association.
  - Kappa (KOP) – dysphoria, some pain relief
    - Stimulate the kappa receptor to get these effects.
    - Drugs that target kappa receptors don't work well because they only offer moderate pain relief and heavy kappa stimulation can cause hallucinations.
  - Delta (DOP) – mild pain relief, antidepressant effects
    - Mild pain relief
    - Not many drugs work with these one
    - Not a typical target
- The medical value of opioids
  - Suppress coughing. One of the early uses (codeine cough syrups).
    - Dr. Upchurch's roommate with poodle: use hydrocodone for annoying poodle in car
  - Control diarrhea. A serious issue! Cholera/diphtheria diseases = lose so many electrolytes/ cannot recover due to this diarrhea. Opioids were of value due to controlling this huge medical problem.
  - Relieve pain
    - Nothing that works better

At this point less addictive drugs can be used for coughing and diarrhea. Pain relief remains a major and currently irreplaceable opioid function.

Opiates are also very good at soothing crying babies, a trick known since ancient Egyptian times, but this is not legal anymore. Example: Mrs. Winslow's Soothing Syrup, a delightful mix of morphine and alcohol that would kill babies by overdose if given at the recommended dose level.

- Dependence on opioids
    - All users, medical or not, are likely to develop tolerance and dependence
    - Part of the nervous system adaptation to these drugs
        - All pain killing drugs = Mu receptor agonists
    - Receptor desensitization
        - Decrease of receptor density
        - NS not very sensitive to own endorphins when you take drug away; ties into withdrawal symptoms
    - Withdrawal syndrome is lengthy and unpleasant, but not lethal

- Withdrawal from heroin or morphine
    - 6 hours after last dose (a.l.d.)
        - Craving
        - Anxiety
        - (Mild discomfort)
    - 14 hours a.l.d.
        - Yawning
        - Perspiration
        - Runny nose
        - Teary eyes
        - (More flu-ish like symptoms)
    - 16 hours a.l.d.
        - All of the above, plus
        - Pupil dilation
        - Goosebumps - quitting cold turkey
        - Tremors
        - Hot and cold flashes
        - Flu-like aching
            - Withdrawal from any painkiller… rebound = pain
        - Loss of appetite
    - 24-36 hours a.l.d.
        - Increased intensity of all of the above, plus
        - Insomnia
        - High blood pressure and pulse rate
        - High temperature
        - High rate of breathing and deeper breaths
        - Restlessness
        - Nausea

- 36-48 hours a.l.d.
  - Increased intensity of the above, plus
  - Curling up position
  - Vomiting
  - Explosive diarrhea -- (** Mu agonists)
  - Weight loss
  - Pain may become intense
  - Muscles may cramp or have spasms - kicking the habit
- 48-72 hours a.l.d.
  - Physical symptoms gradually ease
  - Craving for the drug persists 6 months or longer
  - Even when sick feelings gone, cravings will maintain

Musical and video interlude: https://www.youtube.com/watch?v=mtwFZwjCSTE
This is an actual music video created by Insys Pharmaceuticals. This video was played for the jury in a case in which Insys is charged with creating a kickback scheme for physicians who prescribed the drug. Subsys is a fentanyl oral spray.

Check in here when you're finished with the video, please: Students typed their names below. In addition to letting me know when the class was ready to move on, these sign-ins allowed me to gauge student presence in the class, an important feature since we were using only the audio capabilities of Google Meet.

Student 1
Student 2
Student 3
Student 4
Student 5
Student 6 – Student 9 said what I was thinking Student 9 made an oral comment about the video in addition to the written comment below
Student 7
Student 8
Student 9 hated that (It was funny but TRULY terrifying!!! ALSO FENTANYL ORAL SPRAY?????????) - Sorry. Lets you titrate the dose, that's why "I love titration and it's not a problem" <-- My response to this student.
Student 10
Student 11

Example of the written component of a conversation about the Insys video:
My words: You may be wondering who the audience for this video was. It was developed as an "inspiration" for the sales force, to encourage them to go out and get more doctors onboard, and it was shown at a convention for the Insys sales reps.
A student: Was it really shown to a jury?
My words: Yes. And the end result was that company execs ended up going to jail. (Hah!)
A student: Wow, that's insane.

- Opioid Use Disorder Criteria:
  - A minimum of 2-3 criteria is required for a mild substance use disorder diagnosis, while 4-5 is moderate, and 6-7 is severe (APA, 2013). Opioid Use Disorder is specified instead of Substance Use Disorder, if opioids are the drug of abuse.
  - Taking the opioid in larger amounts and for longer than intended
  - Wanting to cut down or quit but not being able to do it
  - Spending a lot of time obtaining the opioid

- Craving or a strong desire to use opioids
- Repeatedly unable to carry out major obligations at work, school, or home due to opioid use
- Continued use despite persistent or recurring social or interpersonal problems caused or made worse by opioid use
- Stopping or reducing important social, occupational, or recreational activities due to opioid use
- Recurrent use of opioids in physically hazardous situations
- Consistent use of opioids despite acknowledgment of persistent or recurrent physical or psychological difficulties from using opioids
- *Tolerance as defined by either a need for markedly increased amounts to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount. (Does not apply for diminished effect when used appropriately under medical supervision).
- *Withdrawal manifesting as either characteristic syndrome or the substance is used to avoid withdrawal. (Does not apply when used appropriately under medical supervision.)
- *This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.
  - * - opioids are used medically; the person who is using it properly, they are not considered to have substance use disorder even if they meet the criteria.

Round, black and white bullet points below are mine. Square black bullet points and anything under them were added by students.

- Problems with addiction
  - Crime to obtain drugs or the money for them
  - Social disruption – drugs prioritized over family, work, etc. *Dreamland*
  - Overdose-related deaths
  - Stress on health care providers
    - Patient- do they need the painkiller? Or do they just want the drug?
    - Robberies of drugs from pharmacies
    - Fraudulent acts (fake prescriptions & fake injury documentations)
    - People will get angry if they didn't get prescribed the drug
  - Disease transmission esp. with injections
    - AIDS transmission
    - Hepatitis C
    - YOU MUST CARE: bigger public health issue
      - They are literal human beings like yourself stop being judgmental!!

Other health implications

Birth defects

Neonatal abstinence syndrome

- Approaches to addiction
  - Interdiction – keep drugs from entering the country
    - Possible, but difficult, to get rid of shipments of opium
    - People who actually need the medications will be left in a mess
    - But then turn to synthetic drugs
    - Market involved/ smuggling drugs in/ crime rates/ black market issue
    - Criminalizing a drug out of market

        - Treatment of people in terms of drug crimes: harsh criminal implications for being caught with heroin
    - Prohibition and criminalization – imprison drug offenders
    - Harm reduction – address the problems associated with addiction

- Pros and cons of…
    - Opioid maintenance
    - Opioid withdrawal
    - Needle exchange programs
        - Does this help more than the addicts?
        - What are the arguments?
        - Clean needles→ encourage more use?
    - Interdiction programs

We did not have time to get to the questions presented below during this class session.

- What practices should be used in prescribing opioids
    - ...for acute pain? Injury or surgery and have a lot of pain temporarily?
        -
    - …chronic pain without terminal illness?
        -
    - chronic pain with terminal illness?