Benzodiazepines – The Good, the Bad, and the Ugly

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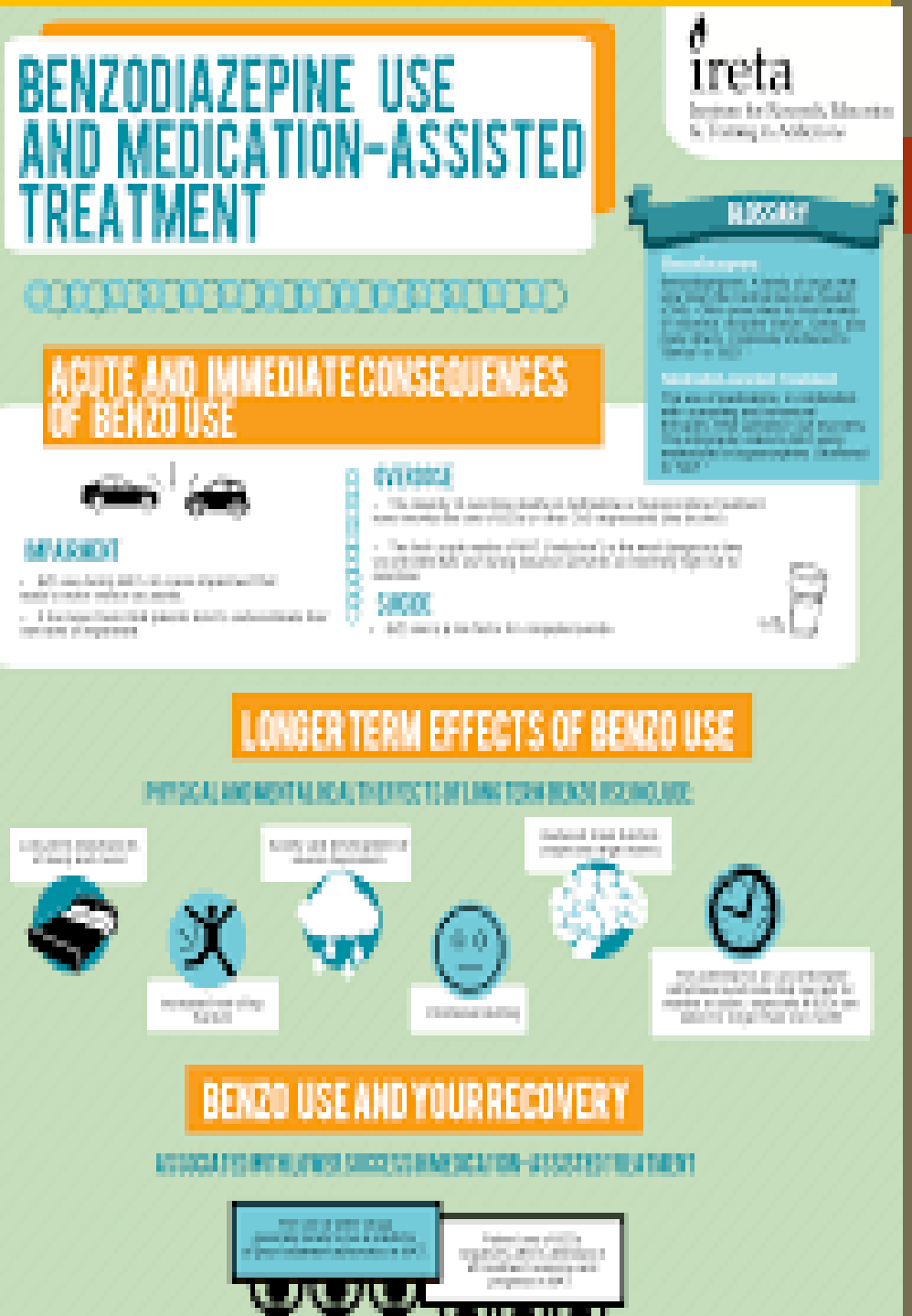


Benzodiazepines – The Good, the Bad, and the Ugly

We are at a time when it is a good thing to evaluate the efficacy of psychotropic medications. This PowerPoint summarizes the work of renowned Professor of Pharmacology, Dr. Robert Raffa, Ph.D., who has devoted much of his distinguished career to researching benzodiazepines and Dr. Christy Huff, cardiologist and benzodiazepine survivor.

Although Dr. Raffa and Dr. Huff acknowledge that benzodiazepines have some use in the very short-term, long-term use can very dangerous and even potentially life-threatening and withdrawal can be beyond your worst nightmare.

Please note that I am not a prescriber, and I am not advising you to take or not take any medication. Rather, I am offering some of the research on the mechanisms and outcomes of benzodiazepine use to help you form your own opinion.

Please visit Dr. Raffa's websites:

https://medicine.arizona.edu/benzodiazepine-withdrawal-symposium/meet-the-speaker

https://www.practicalpainmanagement.com/author/10877/raffa

https://pharmacy.temple.edu/about/school-pharmacy-directory/robert-raffa

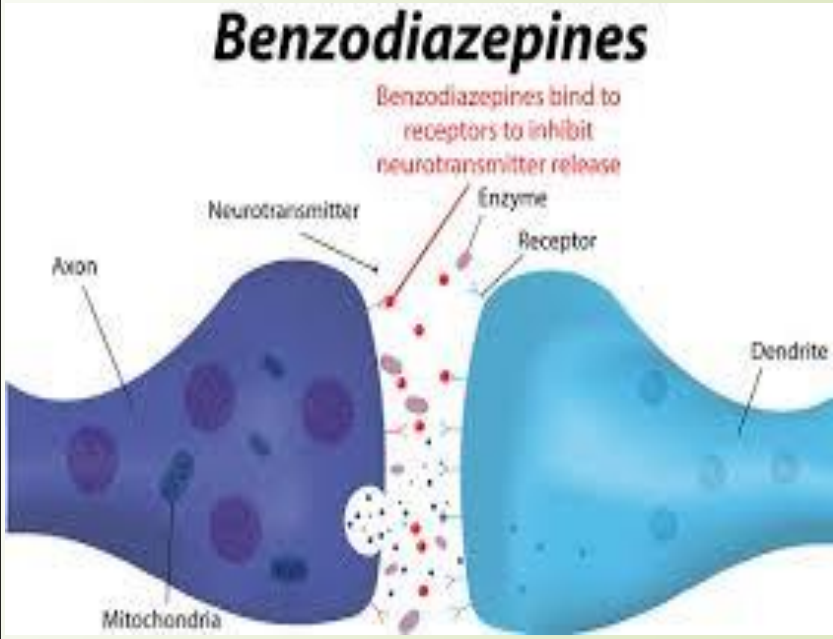

The Alliance for Benzodiazepine Best Practices
Solving the benzodiazepine problem by providing evidence based solutions

What are benzodiazepines:

- A class of psychoactive drugs / tranquillizers with sedative, sleep-inducing, anti-anxiety, anticonvulsant, and muscle relaxant properties

- They target the $GABA_A$ receptor and enhance the effect of the neurotransmitter GABA

- Common Brand names/drug names are Xanax/ Alprazolam, Klonopin/Clonazepam, Valium/ Diazepam, Ativan/ Lorazepam



Benzodiazepines and GABA receptors

McKernan, R. M., Rosahl, T. W., Reynolds, D. S., Sur, C., Wafford, K. A., Atack, J. R., ... & Garrett, L. (2000). **Sedative but not anxiolytic properties of benzodiazepines are mediated by the GABA A receptor α 1 subtype.** *Nature neuroscience*, *3*(6), 587.

Rowlett, J. K., Platt, D. M., Lelas, S., Atack, J. R., & Dawson, G. R. (2005). **Different GABAA receptor subtypes mediate the anxiolytic, abuse-related, and motor effects of benzodiazepine-like drugs in primates.** *Proceedings of the National Academy of Sciences*, *102*(3), 915-920.

Milić, M., Divljaković, J., Rallapalli, S., Van Linn, M. L., Timić, T., Cook, J. M., & Savić, M. M. (2012). **The role of α1 and α5 subunit-containing GABAA receptors in motor impairment induced by benzodiazepines in rats**. *Behavioural pharmacology*, *23*(2), 191.

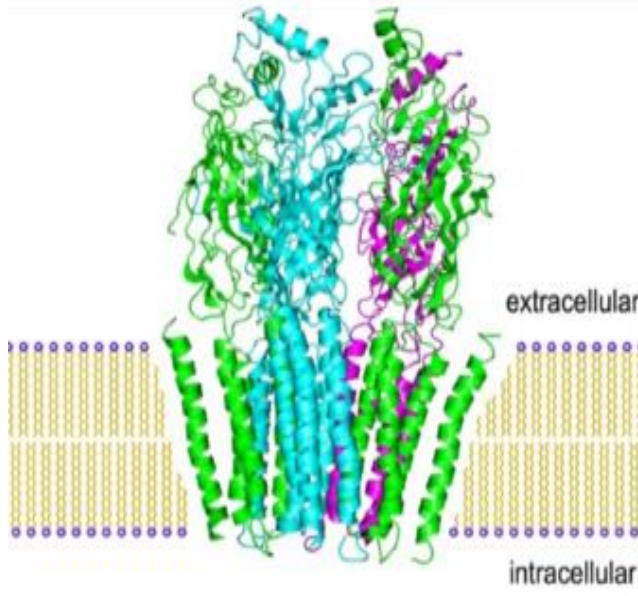
Benzodiazepines impact the GABA receptors

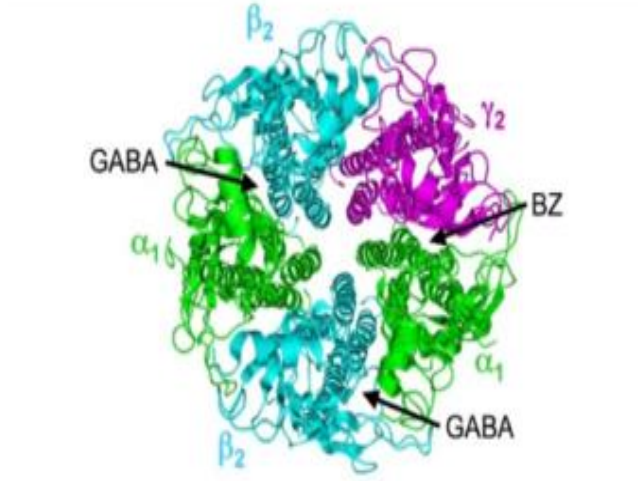
There are about 70 types of benzodiazepines on the market today

Benzodiazepines		
Adinazolam	Cloxazolam	Flunitrazepam
Alprazolam	Delorazepam	Flunitrazolam
Bretazenil	Diazepam	Flurazepam
Bromazepam	Diclazepam	Flutazolam
Bromazolam	Estazolam	Flutoprazepam
Camazepam	Ethyl carfluzepate	Halazepam
Chlordiazepoxide	Ethyl loflazepate	Ketazolam
Cinazepam	Flualprazolam	Loprazolam
Cinolazepam	Flubromazepam	Lorazepam
Clobazam	Flubromazolam	Lormetazepam
Clonazepam	Mexazolam	Meclonazepam
Clonazolam	Midazolam	Medazepam
Clorazepate	Nifoxipam	Quazepam
Nitrazepam	Nimetazepam	Rilmazafone
Nitrazolam	Pinazepam	Temazepam
Nordiazepam	Prazepam	Thienalprazolam
Norflurazepam	Premazepam	Tetrazepam
Oxazepam	Pyrazolam	Triazolam
Phenazepam		

athienotriazolodiazepines
Bentazepam
Brotizolam
Clotiazepam
Deschloroetizolam
Etizolam
Fluclotizolam
Metizolam

Atypical benzodiazepines
DMCM
Flumazenil
Eszopiclone
Zaleplon
Zolpidem
Zopiclone





The most commonly prescribed benzodiazepines and the conditions they are typically prescribed to treat include:

- Xanax (alprazolam) treats anxiety disorders and panic disorder, and sometimes agoraphobia (fear of open spaces), depression, and premenstrual syndrome.
- Klonopin (clonazepam) treats panic attacks and seizures.
- Valium (diazepam) is used to treat anxiety, seizures, muscle spasms, and alcohol withdrawal, as well as IBS and panic attacks.
- Ativan (lorazepam) is primarily prescribed for anxiety, but may also be used for seizures, IBS, insomnia, alcohol withdrawal, and to help nausea and vomiting in people receiving cancer treatments.
- Halcion (triazolam) is used as a short-term treatment for insomnia.

VeryWellMind:

https://www.verywellmind.com/the-benzodiazepines-378909

Other benzodiazepines and the conditions they are typically prescribed to treat include:

- Restoril (temazepam), estazolam, and flurazepam are short-term treatments for insomnia.
- Versed (midazolam) is typically used in children before medical procedures or surgery.
- Librium (chlordiazepoxide) treats anxiety and alcohol withdrawal, as well as IBS.
- Tranxene (clorazepate) is used for anxiety, alcohol withdrawal, and along with other medications to control seizures.
- Oxazepam treats anxiety, alcohol withdrawal, and IBS.

VeryWellMind
https://www.verywellmind.com/the-benzodiazepines-378909

Commonly published side effects:

- Constipation
- Confusion
- Depression
- Diarrhea
- Drowsiness
- Dry mouth
- Erectile dysfunction
- Fatigue
- Headache
- Impaired motor skills and coordination
- Irritability
- Loss of appetite or increased appetite
- Low libido
- Muscle weakness
- Short-term memory loss and impaired cognition

VeryWellMind
https://www.verywellmind.com/the-benzodiazepines-378909

Commonly published long-term side effects may include:

- Acute anxiety
- Agoraphobia (the fear of open or public spaces)
- Anhedonia (the inability to feel pleasure)
- Depression
- Inability to think cohesively
- Loss of libido
- Social phobias

Long-term use of benzodiazepines may trigger a worsening of side effects and, in some cases, **paradoxical side effects,** meaning that you may experience an opposite response to the drug than you previously had. Some of these side effects can adversely affect your mood and behavior, causing an altered perception of yourself, your environment, or your relationships.

VeryWellMind
https://www.verywellmind.com/the-benzodiazepines-378909

Even patients who take benzos “as prescribed” are experiencing disturbing side effects.

Holly Hardman, documentary filmmaker and Massachusetts resident, was one of these patients. Her doctor prescribed her Klonopin for chronic fatigue syndrome and assured her that the drug was perfectly safe to take long-term. But as her tolerance grew, she experienced strange side effects including gastrointestinal issues, panic attacks while driving, and a foggy, “drugged” feeling. However, her doctor never connected her symptoms to the drug, which is a common oversight. It was only when Hardman started researching online that she linked her side effects to Klonopin and created a tapering plan.

It took Hardman almost two years to taper off the drug completely, during which time she experienced even more disturbing side effects such as akathisia, the feeling that you are about to jump out of your skin, and aphasia, the inability to form words and sentences. Even though the withdrawal process was “hellish,” Hardman knows others who had much worse experiences, and many who did not survive coming off of benzos.

It was after this experience, and hearing the experiences of others, that Hardman knew she had to do something. So, she took action in the best way she knew how – by making a documentary film. The film, still in progress, is called As Prescribed. It features the stories of people who thought they were being “good patients” by taking their benzodiazepine prescription and are still dealing with the consequences of side effects and withdrawal (see trailer below).

Link to video trailer made by Holly Hardman of some tortured by benzodiazepines:

https://rightcarealliance.org/article/film-highlights-harm-benzo-overuse/

Benzodiazepines become addictive rapidly

Benzodiazepines and addiction

Heikkinen, A. E., Möykkynen, T. P., & Korpi, E. R. (2009). **Long-lasting modulation of glutamatergic transmission in VTA dopamine neurons after a single dose of benzodiazepine agonists.** *Neuropsychopharmacology*, *34*(2), 290.

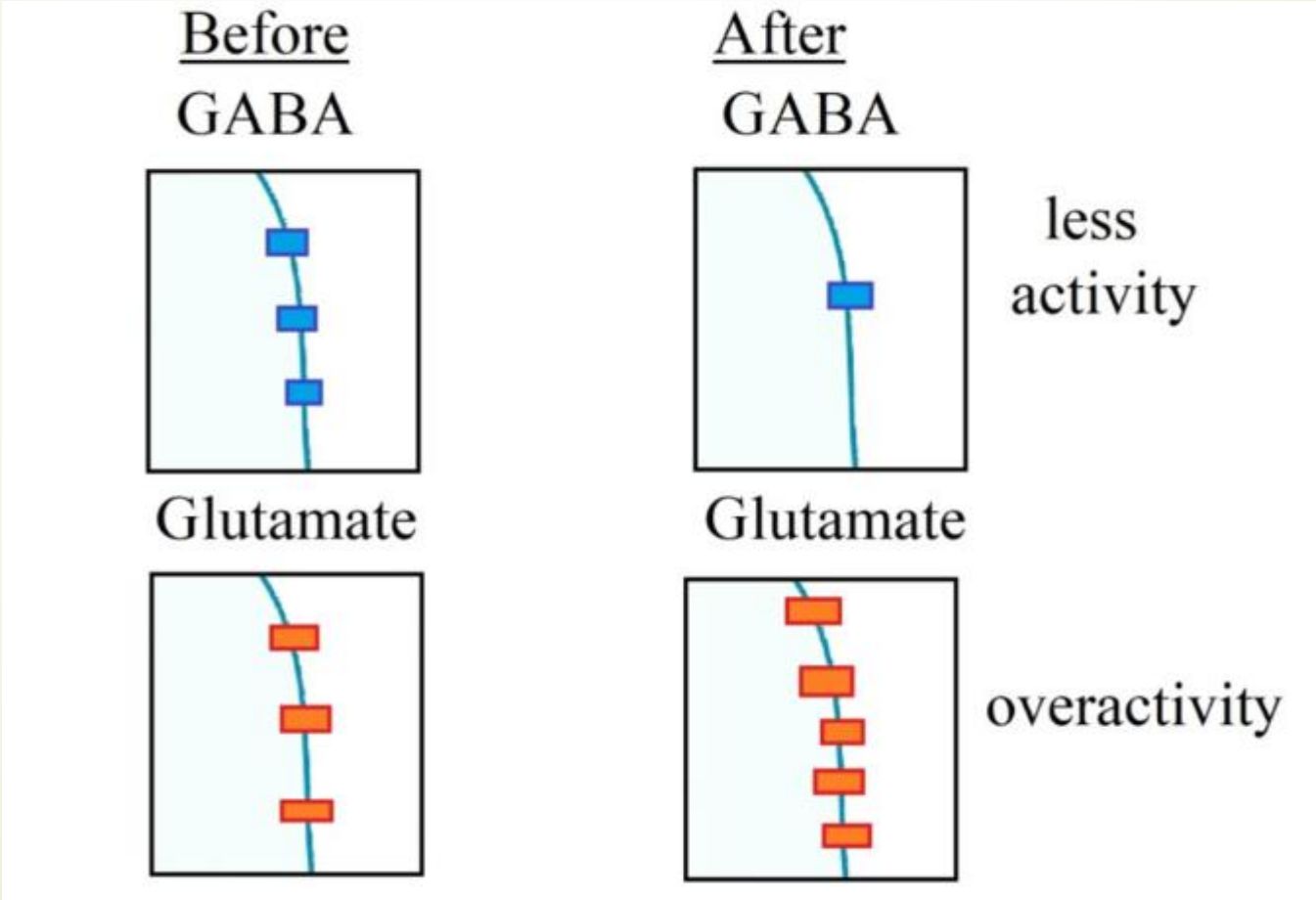
Tan, K. R., Brown, M., Labouèbe, G., Yvon, C., Creton, C., Fritschy, J. M., ... & Lüscher, C. (2010). **Neural bases for addictive properties of benzodiazepines.** *Nature*, *463*(7282), 769.

Tan, K. R., Rudolph, U., & Lüscher, C. (2011). **Hooked on benzodiazepines: GABAA receptor subtypes and addiction.** *Trends in neurosciences*, *34*(4), 188-197.

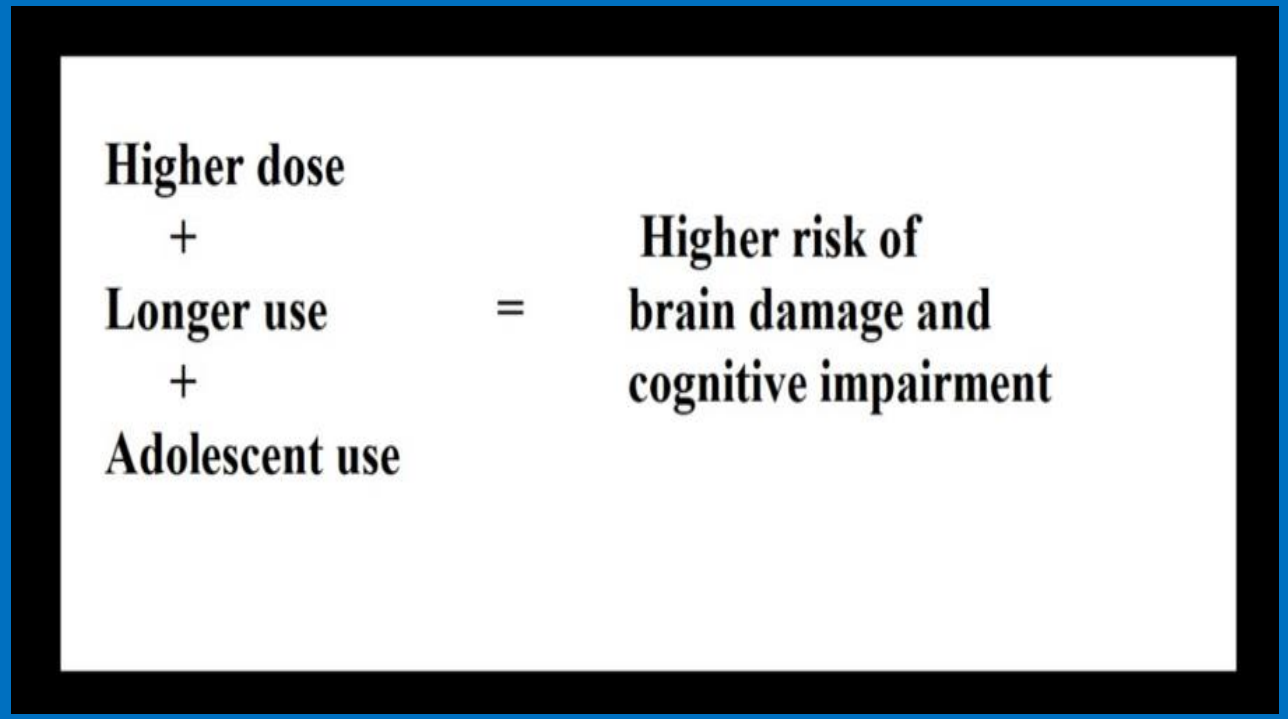
Wafford, K. A. (2005). **GABAA receptor subtypes: any clues to the mechanism of benzodiazepine dependence?**. *Current opinion in pharmacology*, *5*(1), 47-52.

Rada, P., & Hoebel, B. G. (2005). **Acetylcholine in the accumbens is decreased by diazepam and increased by benzodiazepine withdrawal: a possible mechanism for dependency.** *European journal of pharmacology*, *508*(1-3), 131-138.

The brain responds to benzodiazepines by downregulating or decreasing GABA (an inhibitory neurotransmitter) and upregulating glutamate (anexcitatory neurotransmitter)



Common sense as well as science tell us:



True benzodiazepine horror story:

Posted on Trudy Scott's website;

https://www.everywomanover29.com/blog/benzodiazepine-horror-story-on-the-mental-wellness-summit-2

Been totally disabled by benzos for over 3 years. I have been off meds for 17.5 months and the impact of these meds makes any anxiety I ever felt a cake walk.

When I turned 21, I went to the doctor for dizziness, and they put me on Xanax. I started to feel anxious, and they then added Zoloft. That was the start of a long journey. I was shifted from one anti-depressant to another. At 34 I was told I was treatment resistant, and they added lamotrigine. Then my world crashed at age 37. I have been on Xanax, then Klonopin, then Ativan, then back to Xanax, then Valium to taper. I had also been given Ambien to sleep in early 30s.

I tapered off meds over a period of a year. I was on 1.5 mg Xanax and tapered off Valium as prescribed. I have tried many supplements, but I react poorly to all of them. I get very agitated and revved up.

I have locked shoulder muscles, neck, jaw; I have internal vibrations, I get bad headaches, jelly legs, distorted vision like floaters and squiggles and fireworks, my teeth all feel like they will fall out, but they are not loose, it feels like adrenaline or cortisol rushes through the body. Sometimes my arms go numb. I am pretty tortured every day. These meds are truly causing chemical warfare on some of us.

By way of transparency and authenticity, I suffered greatly from benzodiazepine use many years ago. This came, when midway through life, I was hit with a series of stressors that my weakened emotional constitution, due early trauma, could not handle. My wife had just recovered from cancer, my daughter was being evaluated for what was thought to be lymphoma, my Marine son was dodging IEDs in Iraq, a client of mine was making threats to destroy my career (normally I would have shrugged this off, as my clinical performance in this case was in good standards of practice), and the financial crisis of 2008 hit and, holding considerable real estate properties which plummeted in worth, we were brought to the brink of bankruptcy. After weeks with little to no sleep, I came to a point of complete emotional collapse. As part of my therapy, I was prescribed a combination of antidepressant medication and benzodiazepines. The relief of the benzodiazepine therapy was immediate and very helpful. I continued this medication exactly as prescribed and, after an extended time of being on it and after I had largely recovered, my anxiety and a new problem, akathisia, which is a little-known side effect of certain medications, most commonly anxiolytics, antipsychotics and antidepressants, and is characterized by extreme inner restlessness. For some, the turmoil is so strong it quickly leads to death by suicide. For me, the impact of benzodiazepines short-term was excellent, but long-term use almost destroyed me. Although I have, happily, completely recovered and have been medication free for many years now, titrating off this medication was nothing short of neurological hell. I have since learned that many others have suffered similarly or, far worse. Tragically, some have even lost their lives.

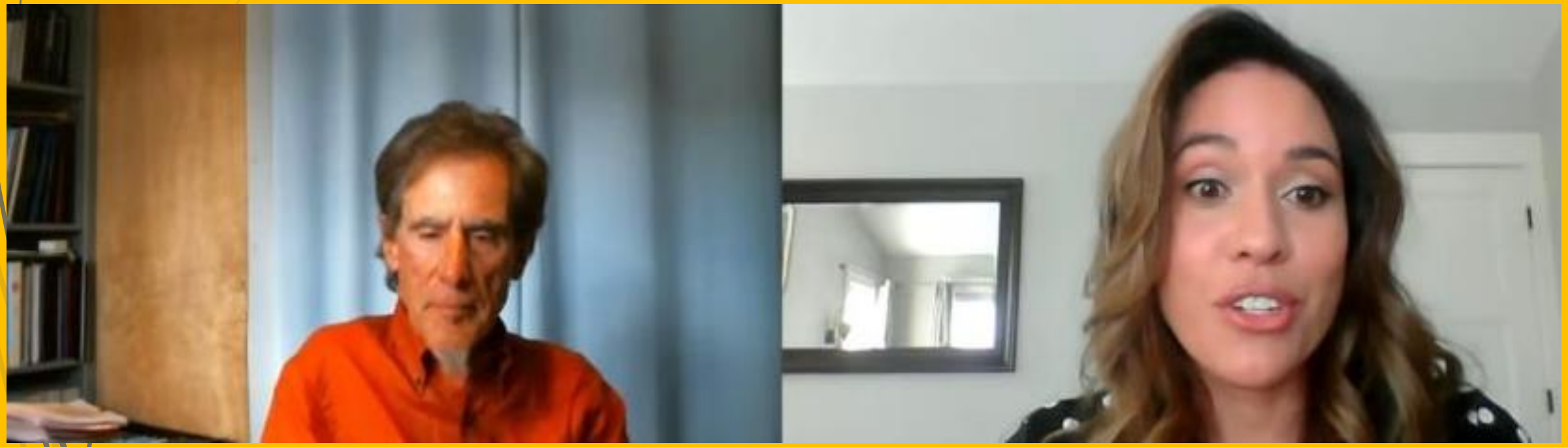
Akathisia, a common side effect of benzodiazepines – If there were an equivalent of neurological hell, this would be it

AKATHISIA is a combination of subjective feelings of restlessness/agitation and a compelling need to move, rock or pace.

Signs & Symptoms Can Include:

- A sense of inner restlessness
- An intense feeling of agitation
- Non-productive, often uncontrollable movements including rocking, pacing and shifting weight. Movements do not give relief
- Suicidal/homicidal ideation

Dr. Robert Raffa and interviewer, benzodiazepine survivor, advocate, and Mad in America blogger/YouTube host, Jocelyn Pedersen. The content of the first segment of this PowerPoint draws almost exclusively from their interview.



Click here to view the entire content of this informative interview:

https://www.youtube.com/watch?v=FgqrwgmK0as

Click here to access Jocelyn Pedersen superlative website,

Benzo Brains

https://www.madinamerica.com/2017/07/youtube-channel-benzo-brains/

About Dr. Robert Raffa

- **Robert B. Raffa, PhD** has devoted his professional career to pharmacology and understanding the balance between therapeutic utility and abuse potential of medications. He was team co-leader for analgesics drug discovery at Johnson & Johnson. Dr. Raffa has received more than $3 million in research funding from National Institutes of Health and other sources for the investigation of drug action and drug abuse issues. Dr. Raffa has published over 300 peer-reviewed papers, is the co-author or editor of several books on pharmacology and thermodynamics and is a co-editor of the Journal of Clinical Pharmacy and Therapeutics. He is a past president of the Mid-Atlantic Pharmacology Society, and he lectures and consults worldwide on analgesic drugs and analgesic combinations.

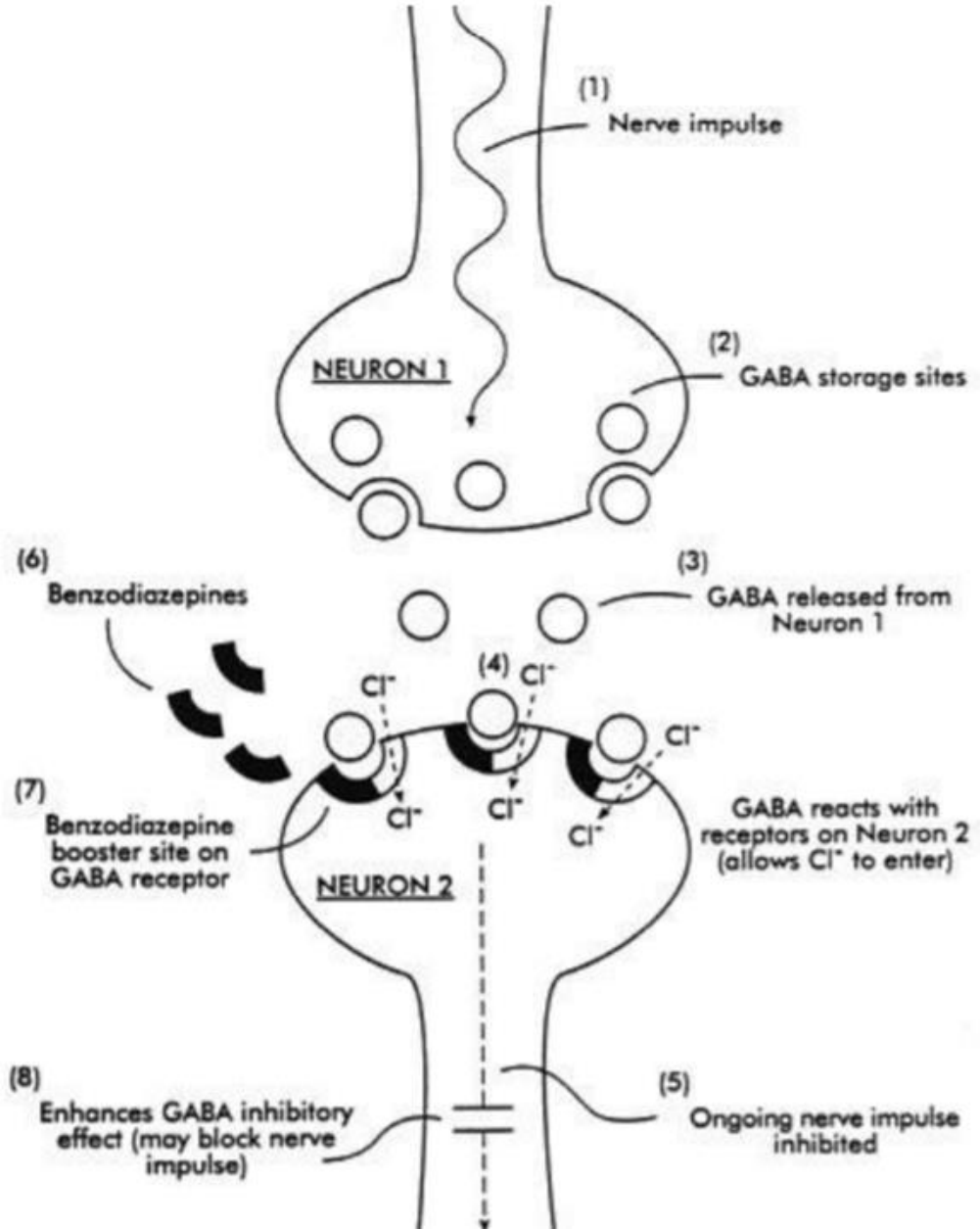
A *New Perspective* on the Pharmacology of BZD and 'Z' Drugs

Robert B. Raffa, PhD

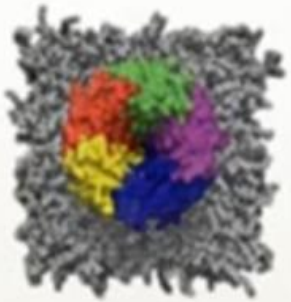
Professor Emeritus, Temple University School of Pharmacy, Philadelphia PA;
Adjunct Professor, University of Arizona College of Pharmacy, Tucson AZ

Mechanism of Action of Benzodiazepines

ig. 1. Diagram of mechanism of action of the natural neurotransmitter GABA (gamm minobutyric acid) and benzodiazepines on nerve cells (neurons) in the brain



From the perspective of anxiety



1843

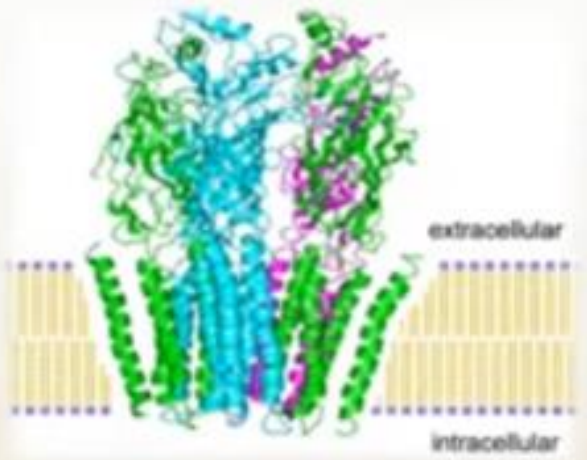
Panphobia – from *The Physiognomy of Mental Diseases* by Alex. Morison

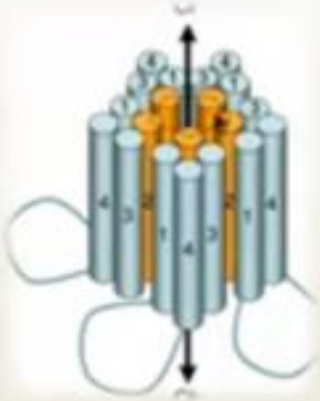
1977

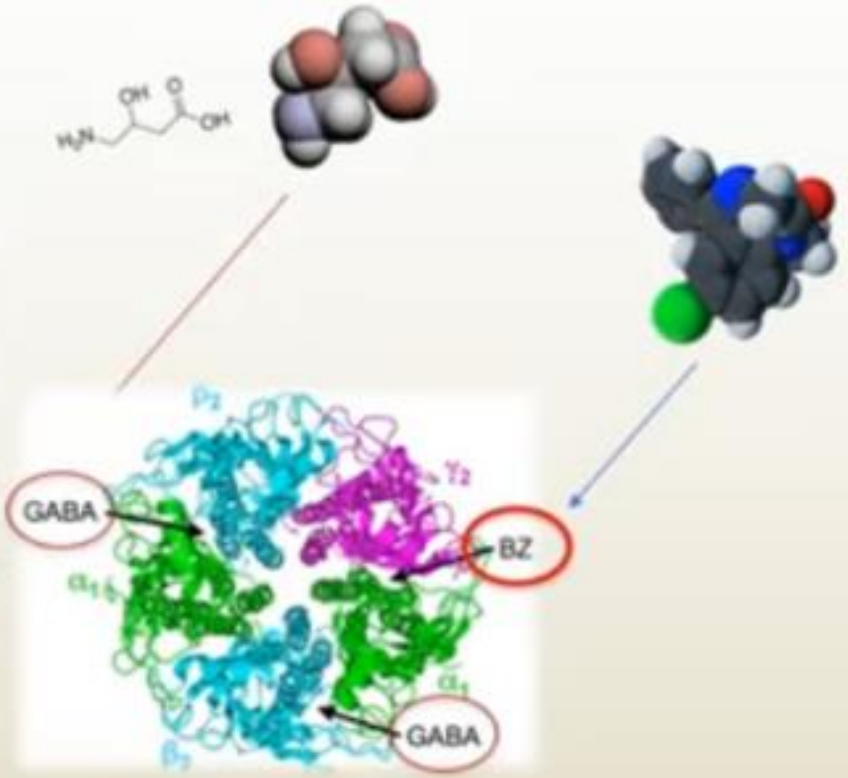
Discovery of brain $GABA_A$-R

https://en.wikipedia.org/wiki/Panphobia

From the perspective of anxiety *(cont'd)*



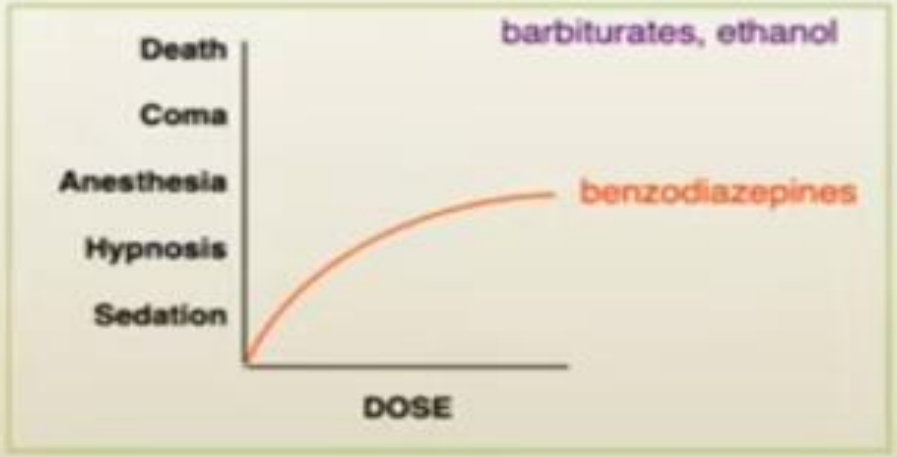




BZDs from the perspective of anxiety – *the good*

- Before: anxiety was a nebulous clinical situation ('psychological', 'neurosis')
  - if 'treated', prescribed barbiturates or other non-specific agents
- After: certain anxiety conditions viewed to be endogenous, *i.e.*, to have a biochemical cause or correlation
  - provided the hope of a mechanistic target
  - stimulated basic science studies of roles of GABA and $GABA_A$-R
  - more selective 'anxiolytic' action
  - safer alternatives to barbiturates (better 'therapeutic ratio')

More specific to anxiety & Fewer AE's

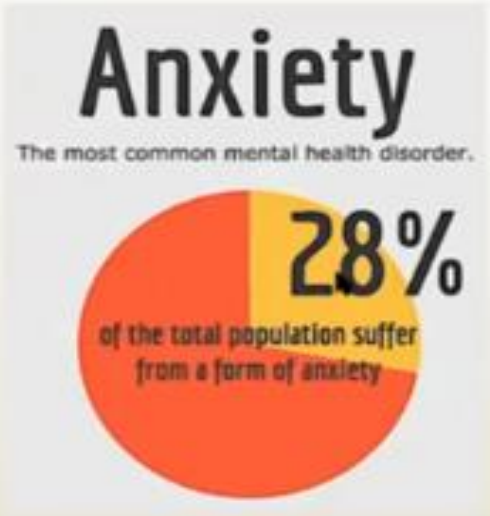


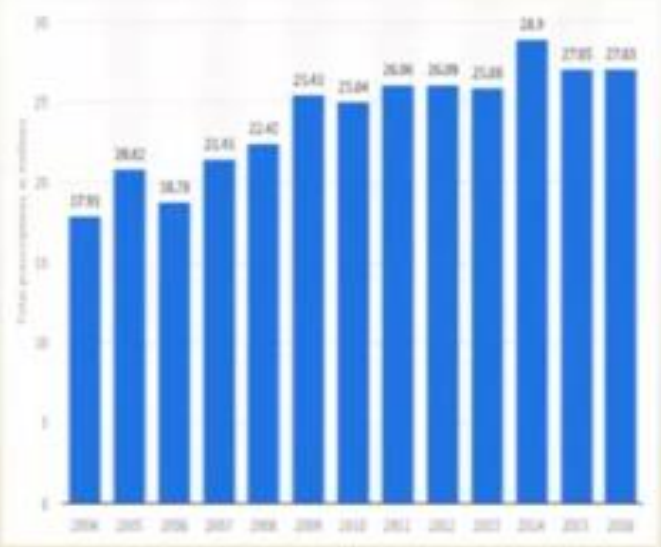
BZDs from the perspective of anxiety – *the bad*

- Motor vehicle crashes
- Hip fractures
- DDIs with CNS depressants (FDA warning with opioids)
- Withdrawal
  - 1963 – chlordiazepoxide (Greenblatt & Shader)
  - 1980 – diazepam (Winokur *et al.*)

BZDs from the perspective of anxiety – *the bad*

- Success breeds over-estimates → over-confidence → inappropriate-use/sales





https://sites.google.com/site/thesixtieswrt104/deliverables
https://www.advancedpsychotherapeutics.com/ANXIETY.en.html
www.statista.com/statistics/781816/alprazolam-sodium-prescriptions-number-in-the-us/

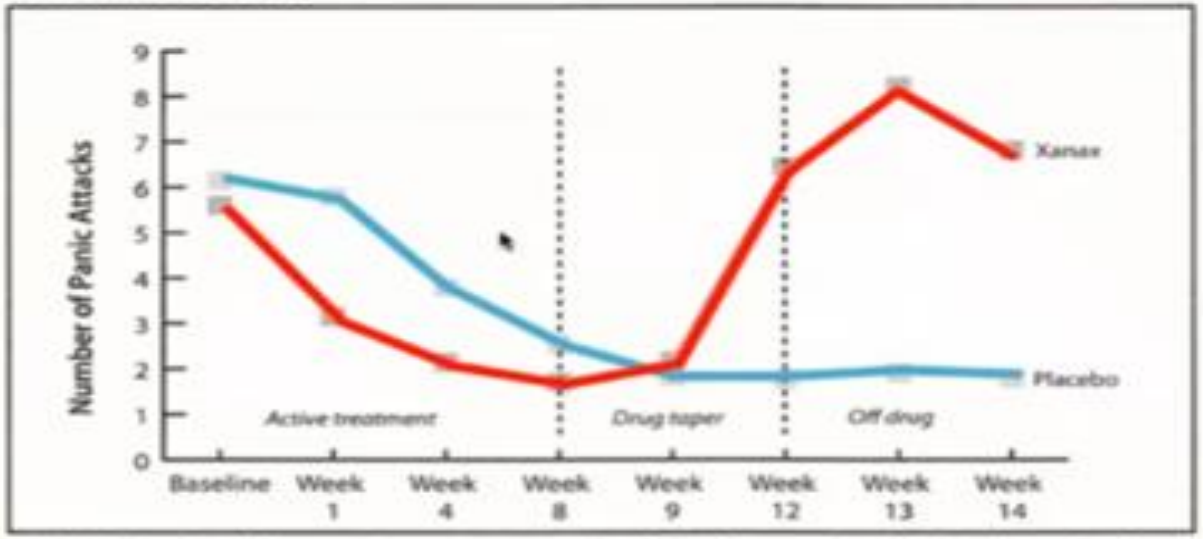
Follow-up studies at 4 weeks show positive effect of the benzodiazepine Zanax but at 8 weeks the positive impact goes sour. The marketers of the drug only reported 4 weeks which, when discovered, resulted in well-deserved lawsuits.

BZDs from the perspective of anxiety

– *the ugly*

- Loosing ground

The Xanax Study



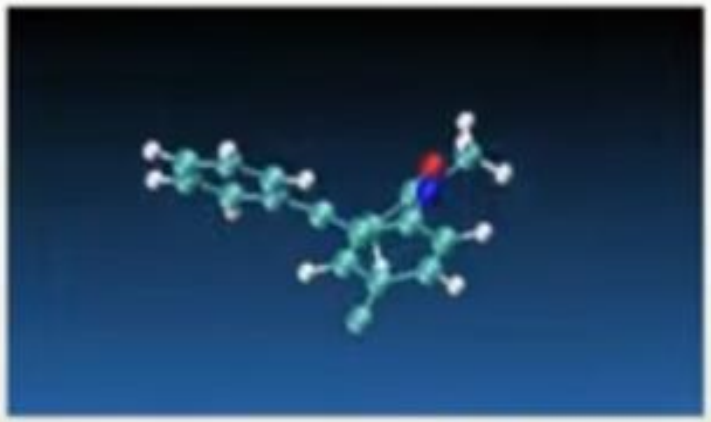
In Upjohn's study of Xanax, patients were treated with the drug or placebo for eight weeks. Then this treatment was slowly withdrawn (weeks 9 through 12), and during the last two weeks patients didn't receive any treatment. The Xanax patients fared better during the first four weeks, which is the result that the Upjohn investigators focused on in their journal articles. However, once the Xanax patients began withdrawing from the the drug, they suffered many more panic attacks than the placebo patients, and at the end of the study were much more symptomatic. Source: Ballenger, C. "Alprazolam in panic disorder and agoraphobia." *Archives of General Psychiatry* 45 (1988): 413–22. Pecknold, C. "Alprazolam in panic disorder and agoraphobia." *Archives of General Psychiatry* 45 (1988): 429–36.

BZDs from the perspective of anxiety – *the ugly*

- Prescriptions extended beyond product labels and testing data
- Healthcare providers flying blind w/o evidence-based studies
- Lack of GRADE* methodology Guidelines
- Murky clinical knowledge base beyond 4-6 weeks
- Murky basic science knowledge base beyond 4-6 weeks
- In fact, murky basic science knowledge <u>about BZDs</u>

*Grading of Recommendations Assessment, Development and Evaluation – http://www.gradeworkinggroup.org/

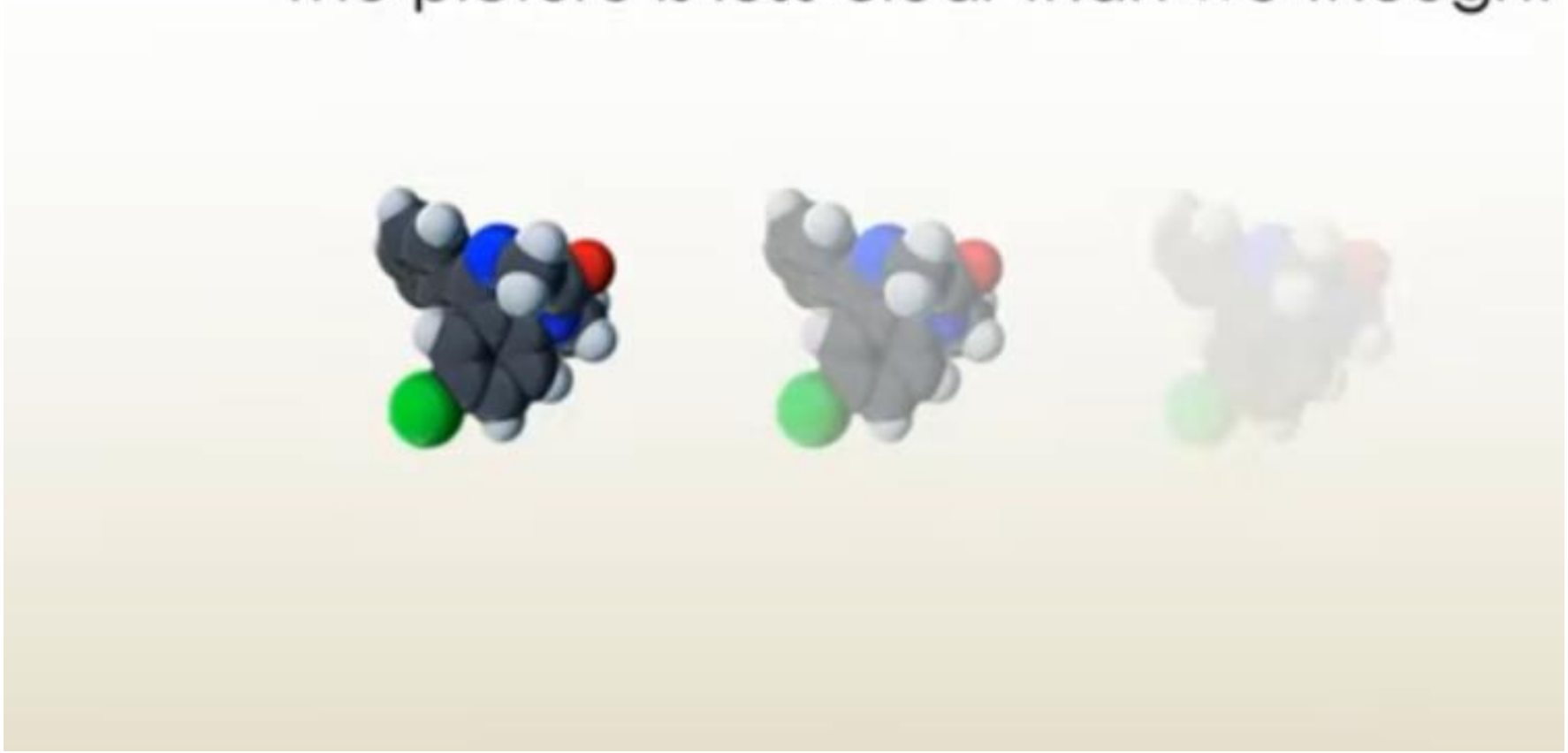
A new perspective: From the viewpoint of pharmacology



From the perspective of pharmacology

https://en.wikipedia.org/wiki/Paraphobia
https://blog.wellcome.ac.uk/2014/06/20/image-of-the-week-gaba-receptor/

The picture is less clear than we thought

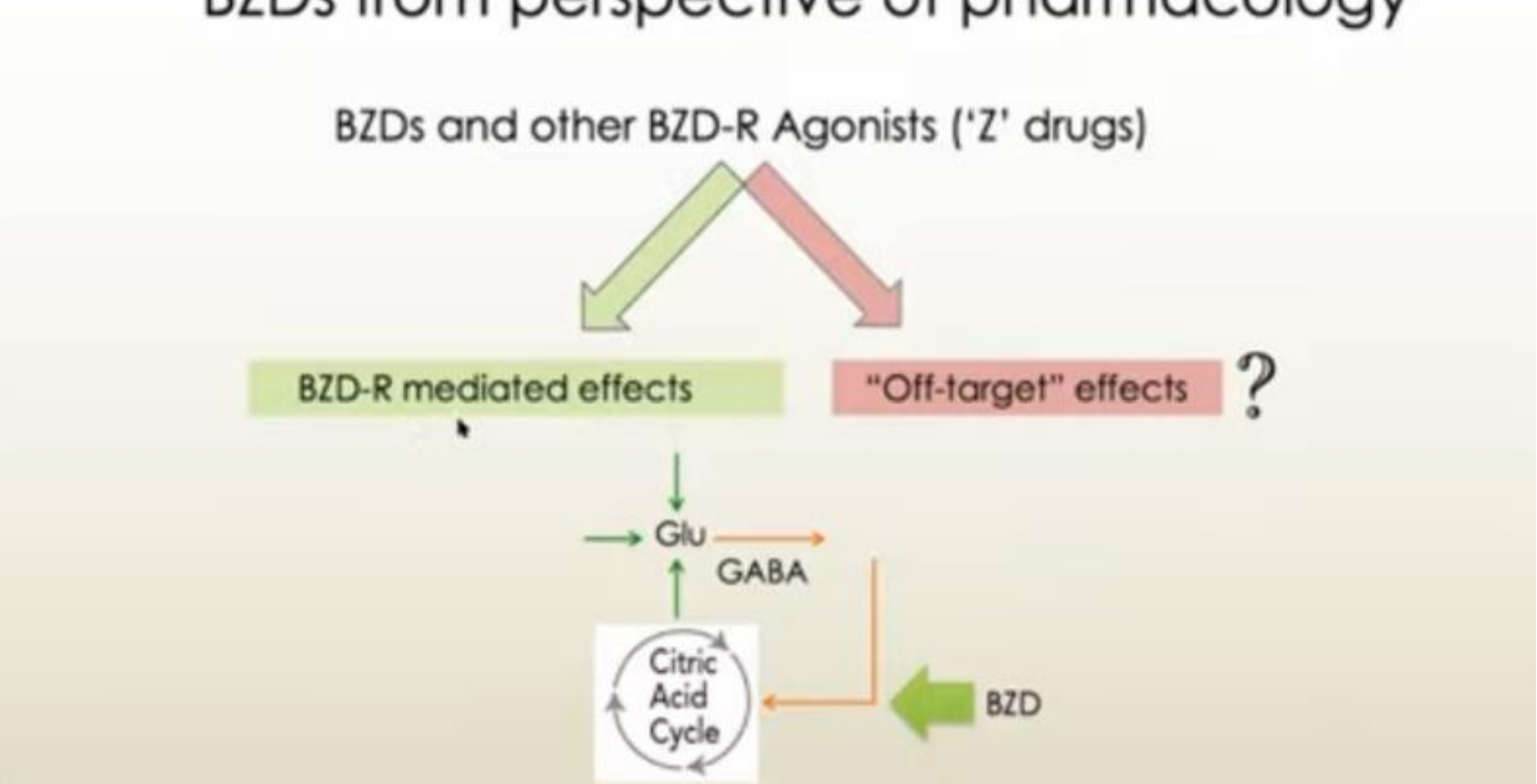


BZDs from perspective of pharmacology

- Receptor binding profile
  - BZD-R – *lots of data – biological effects clear*
  - Other receptors – *paucity of information – biological effects unknown*
- BZDs potentiate adenosine A_{2A} receptor-mediated action by inhibiting the nucleotide reuptake transporter (the 1° mechanism of adenosine degradation), some BZDs more than others[1] – what effects? long-term?
- Diazepam modulates α_1-adrenoceptor signaling by inhibiting phosphodiesterases[2] – what effects? long-term?
- *etc.?*

[1]Seubert *et al.* (2000) *Anesthesiol* 92:567-77
[2]Williams *et al.* (2018) *Pharmacol Res Perspect* e00455

BZDs from perspective of pharmacology



The symptoms in red are not due to the impact of benzodiazepines on the brain but rather on peripheral sites in the body which suggests that this drug effects the whole body in a significantly problematic manner not previously understood.

The following slides a largely from the work of cardiologist, Dr. Christy Huff and her coalition - benzodiazepine survivor and now board member of the Benzodiazepine Information Coalition

- Dr. Huff experienced benzodiazepine withdrawal firsthand after she was prescribed Xanax for insomnia related to a major health crisis in 2015. After developing concerning symptoms and receiving no answers from her primary care doctor and a prominent neurologist, she began to research benzodiazepines and discovered her symptoms were consistent. with benzodiazepine withdrawal syndrome.

- With the help of a local psychiatrist, she slowly tapered off benzodiazepines using Valium over a three-year period. Christy's personal experience has led her to realize the dangers of these drugs and the severity of the benzodiazepine withdrawal syndrome, neither of which were emphasized during her medical training. She is an advocate of better education of physicians regarding the dangers of benzodiazepines and how to safely taper patients off these drugs, and stronger regulation of the prescribing of benzodiazepines.

Please visit Dr. Huff's website:
https://www.benzoinfo.com/benzodiazepine-basics/

GAPS IN PHYSICIAN EDUCATION

- Stopping benzodiazepines abruptly or tapering too quickly
  - Best practice is a flexible, gradual taper plan tailored to patient symptoms
  - May take months or years
- Not recognizing adverse effects (i.e. tolerance, physical dependence, and withdrawal)
  - Assumed to be return of original condition or new illness
  - Leads to unnecessary testing and treatment, polydrugging
- Conflation of addiction with physical dependence
- Lack of informed consent
- Little awareness of protracted withdrawal syndrome

BENZODIAZEPINE INFORMATION COALITION

BENZODIAZEPINE INJURY SYNDROME

- A subset of patients (10-15%) withdrawing from benzodiazepines experience a protracted course (lasting years, possibly permanent in some cases) [1]
- Symptoms can be disabling, and often present in a pattern of "waves and windows"[2]
- Relentless nature of symptoms, plus lack of support/treatment increases risk of suicide
- Long-term use of benzodiazepines can alter conformation of the GABA receptor, causing functional changes in the nervous system
- Further research is need to determine who is at risk
  - Abrupt cessation/rapid taper
  - Kindling phenomenon
  - Genetics

1. Ashton H. J Subst Abuse Treat 1991;8:19-28.

2. Wright S. Benzodiazepine withdrawal:Clinical aspects. In: *The Benzodiazepines Crisis: The Ramifications of an Overused Drug Class*. New York, NY: Oxford University Press; 2020:117-148.

Functional Brain Changes due to Benzodiazepines

The early work of Professor Malcolm H. Lader and his colleagues **documented the first indication of anatomical brain changes** (click for link) associated with benzodiazepines using computed axial tomography (CAT scan), which revealed abnormalities in at least half of the patients examined in the study, with two patients having definite cortical atrophy. The patients were either dependent on or experiencing a protracted withdrawal syndrome from, benzodiazepines. The results warranted further research as they were suggestive of brain damage.

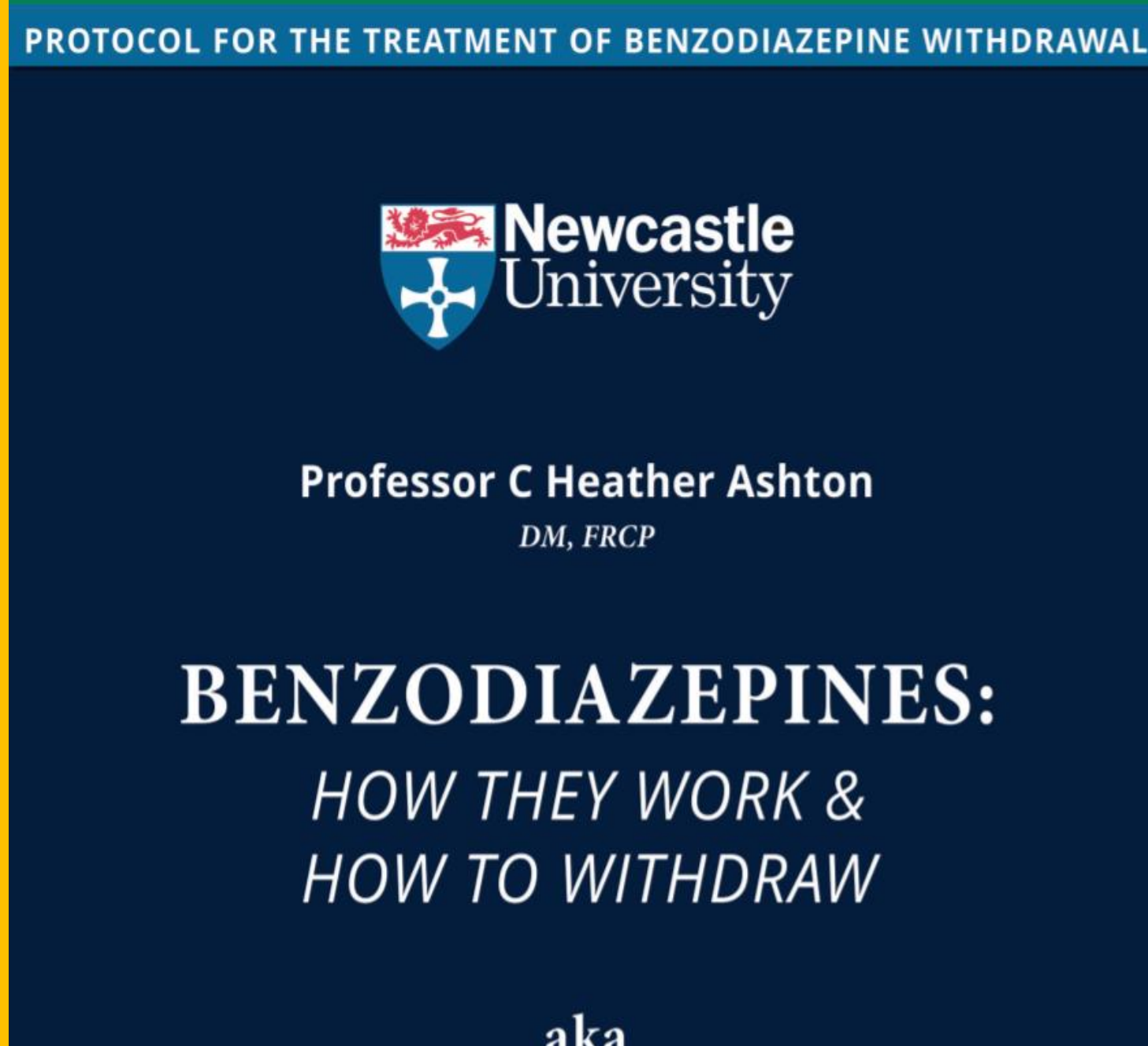
Functional Brain Changes due to Benzodiazepines

Perceptual and sensory disturbances suggest a hyperexcitable central nervous system while recovering from benzodiazepine exposure and cessation. Problems with balance, hearing, tinnitus, and hypersensitivity to sound (hyperacusis) suggests possible vestibular involvement – the part of the brain that's connected to the inner and middle ear. Hypersensitivity to touch, smell and light can also occur. To be understood, these phenomena require more research, but the documentation of their existence adds to the overwhelming amount of evidence that medication physical dependence and discontinuation (withdrawal) can significantly impact functional brain activity on a cellular level.

Should you or your loved one wish to get off benzodiazepines, consult with your prescriber first and consider following the guidelines of the Ashton Manual published in 1999. It has become a cornerstone for people all over the world dealing with benzodiazepine dependence.

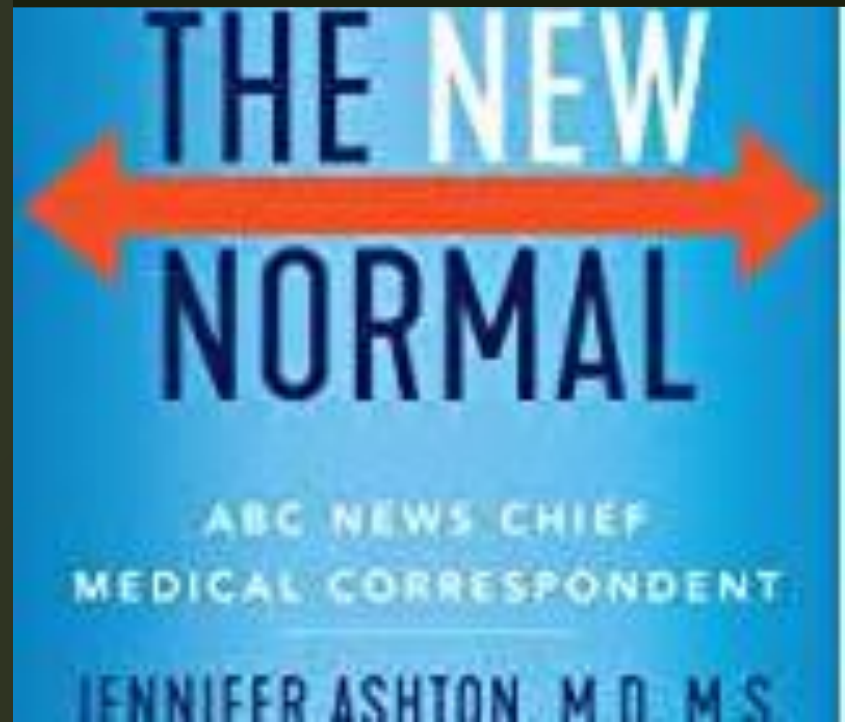
Link to the Ashton Manual:

https://www.benzoinfo.com/wp-content/uploads/2020/08/Ashton-Manual.pdf



About Dr. Heather Ashton:

- Dr. Ashton worked at the University of Newcastle upon Tyne as researcher (Lecturer, Senior Lecturer, Reader and Professor) and clinician since 1965, first in the Department of Pharmacology and latterly in the Department of Psychiatry. Her research centered, and continues, on the effects of psychotropic drugs (nicotine, cannabis, benzodiazepines, antidepressants and others) on the brain and behaviour in man. Her main clinical work was in running a benzodiazepine withdrawal clinic for 12 years from 1982-1994.
- Professor Ashton is a graduate of the University of Oxford and obtained a First-Class Honors Degree (BA) in Physiology in 1951. She qualified in Medicine (BM, BCh, MA) in 1954 and gained a postgraduate Doctor of Medicine (DM) in 1956. She qualified as MRCP (Member of the Royal College of Physicians, London) in 1958 and was elected FRCP (Fellow of the Royal College of Physicians, London) in 1975. She also became National Health Service Consultant in Clinical Psychopharmacology in 1975 and National Health Service Consultant in Psychiatry in 1994. She passed away in 2019 at the age of 90.



In Conclusion:

- To restate my opening comment, I am not recommending that you or your loved one take or not take any medication. Rather, I suggest that you apprise yourself of the outcome research as best you can before you take any psychotropic medication. Empower yourself to ask your prescriber about any concerns you might have to include the content of this PowerPoint. Dr. Robert Raffa, Dr. Huff and many others have done us a great service in offering the good, the bad, and the ugly about short-term and long-term benzodiazepine use and I believe that we owe them much gratitude for their courage in challenging us on the need for thoughtful consideration before we embark down the medication highway.