



Update on the Treatment of Generalized Anxiety Disorder and Panic Disorder: A Focus on the Role of Benzodiazepines

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Disclosure

- I have no actual or potential conflict of interest in relation to this activity.
- I do plan on discussing unlabeled or investigational uses of a commercial product.





Goals: to review the recommendations of evidenced based guidelines and reviews regarding the treatment of generalized anxiety disorder (GAD) and panic disorder (PD). Additionally, we will discuss the preferred role of benzodiazepines for these disorders.

Objectives: by the end of this presentation the participants will be able to:

- List the signs and symptoms of GAD and PD,
- Describe the standard guideline recommendations for acute and maintenance therapy for GAD and PD,
- Demonstrate the role of benzodiazepines in the treatment of GAD and PD, and
- Develop a plan to enhance appropriate evidence based pharmacotherapy for the treatment of GAD and PD.



Generalized Anxiety Disorder (GAD)



- Excessive anxiety and worry more days than not for at least 6 months
- Anxiety is difficult to control
- Anxiety and worry are associated with three or more of the following
 - ❖ Restlessness or feeling keyed up
 - ❖ Easily fatigued
 - ❖ Difficulty concentrating
 - ❖ Irritability
 - ❖ Muscle tension
 - ❖ Difficulty falling or staying asleep
- Anxiety and physical symptoms are impactful on daily living.



Adapted from DSM-V

GAD

- Lifetime prevalence of 5%
 - ❖ 12 month prevalence of 3%
- Higher rates of cardiovascular disease and irritable bowel syndrome
- Females > Males
- Frequently seen in primary care manifest with
 - ❖ Headaches, palpitations, sweating and GI disturbances (primarily diarrhea)

Kessler R. Arch Gen Psychiatry. 2005.
Lieb R. Eur Neuropsychopharmacol. 2005.

Panic Attacks



Period of intense fear in which 4 of the following symptoms develop abruptly and reaches a peak within minutes.

- Palpitations
- Sweating
- Trembling
- Shortness of breath or smothering
- Feeling of choking
- Chest pain
- Nausea
- Dizzy or lightheadedness
- Chills or heat sensations
- Paresthesias
- Derealization or depersonalization
- Fear of losing control
- Fear of dying



Panic Disorder



- At least one of the attacks has been followed by 1 month of one of the following
 - ❖ Persistent concern about having additional attacks or their consequences.
 - ❖ Significant change in behavior related to the attacks

Adapted from DSM-V



Panic attack and Panic Disorder

- >20% experiences a single panic attack in their lifetime.
- Panic disorder lifetime prevalence 5%
- Highest familial link of any anxiety disorder

Martin, et al. Clinics of N. Amer. 2009.
Katzmann MA. BMC Psychiatry. 2014.




Neuropathology of anxiety

- Decreased GABA receptor density.
- Decreased 5-HT
- Increased glutamate

- CO₂ serum concentration sensitivity (panic)
- Increased amygdala activity

- Strong genetic trends
 - ❖ Clear environmental role



Klein D. J Clin Psychiatry. 1996.
Martin EI. Psychiatric Clinics of NA. 2009.

GABA agonism

- Approx 19 subtypes
 - ❖ GABA_A
 - α 1-6, β 1-3, γ 1-3, δ , ϵ , θ , π , ρ 1-3
 - ρ 1-3 sometimes referred to as GABA_C
 - ❖ GABA_B
 - 1 and 2

Rudolph U. Curr Opin in Pharmacol. 2006.
Whiting PJ. Curr Opin in Pharmacol. 2006.
Bowery NG. Curr Opin in Pharmacol. 2006.

GABA receptor subtype and effect

- GABA_A
 - ❖ $\alpha 1$
 - Sedative/hypnotic, reinforcing
 - ❖ $\alpha 2$ and 3
 - Anxiolytic, anticonvulsant ($\alpha 2$)
 - ❖ $\alpha 5$
 - Learning and memory
 - ❖ $\beta 3$
 - Respiratory drive, hypnotic
- GABA_B
 - ❖ Muscle relaxant

Fradley RL. J Psychopharmacology. 2007. Rudolph U. Current Opin Pharmacology. 2006.
Bowery NG. Current Opin Pharmacology. 2006.

BZD MOA

- Benzodiazepines bind to the $GABA_A \alpha 1, 2, 3 \beta 2 \gamma 2$ area.
 - ❖ Results in GABA binding more potently to the receptor.
 - ❖ Increased GABA effect.
 - GABA must be present as BZDs do not have intrinsic agonist activity.

Rudolph U. Current Opin Pharmacology. 2006.

Antidepressant MOA

- Increases 5-HT in the synapse.
 - ❖ Results in neuronal adaptation.
 - Explains delay in efficacy.
- Increased 5-HT is allowed to attach to all 5-HT receptors.
 - ❖ Currently, 15 different receptors have been identified.
 - ❖ 5-HT 1 and 2 families most likely involved with anxiety.

Glennon RA. in Foyes Principles of Med. Chem. 2013.
Stahl S. Stahl's Essential Psychopharmacology. 2013.



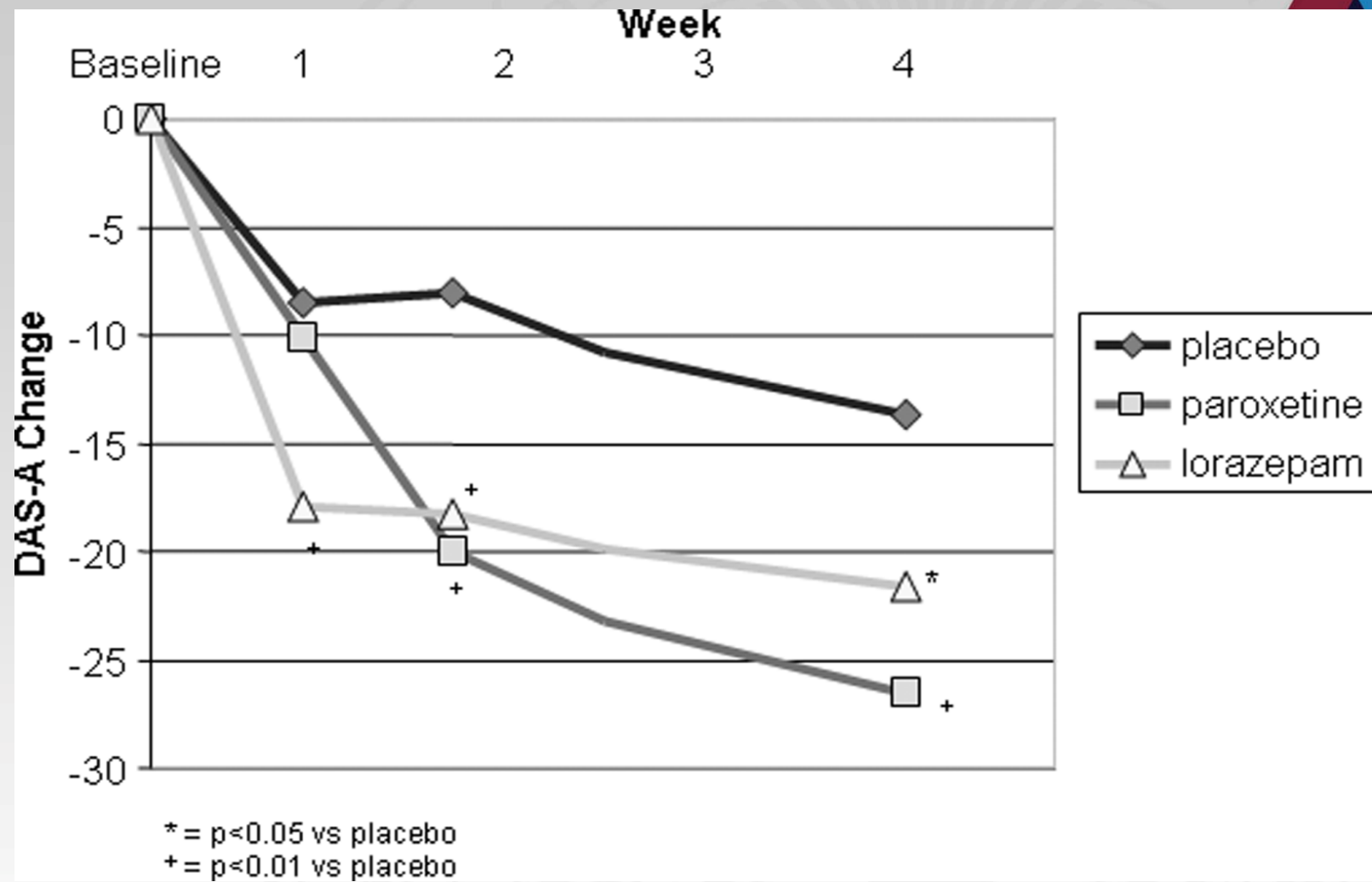
SSRI v BZD for GAD



- Paroxetine (20mg qam) v lorazepam (1.5mg tid) v placebo
- Reduction in DAS-A on:
 - ❖ 24h parox -5.2 lor -12.7 plac -3.8
 - ❖ Day 6 parox -8.3 lor -15.0 plac -7.8
 - ❖ Day 14 parox -20 lor -19 plac -7
 - ❖ Day 28 parox -22.1 lor -20.7 plac -13
- Somnolence parox 29% lor 55%
- Dizziness parox 16% lor 23%
- Nausea parox 18% lor 11%



Feltner DE. CNS Neuroscience and Therapeutics. 2009.



Observed cases

Feltner DE. CNS Neuroscience and Therapeutics. 2009.

SSRI v BZD for PD



- Paroxetine 40mg v clonazepam 2mg
- Reduction in panic attacks per week
 - ❖ baseline parox 5.3 clonaz 5.4
 - ❖ wk 1 parox -4.3 clonaz -4.6
 - ❖ wk 2 parox -4.6 clonaz -4.8
 - ❖ wk 4 parox -4.8 clonaz -5.3
 - ❖ wk 8 parox -5.1 clonaz -5.2
- wk 8 # panic attacks/wk
 - ❖ parox 0.2 clonaz 0.2
- wk 8 % panic free in last week
 - ❖ parox 80% clonaz 89%



Nardi AE. Braz J Med Biol Res. 2011.



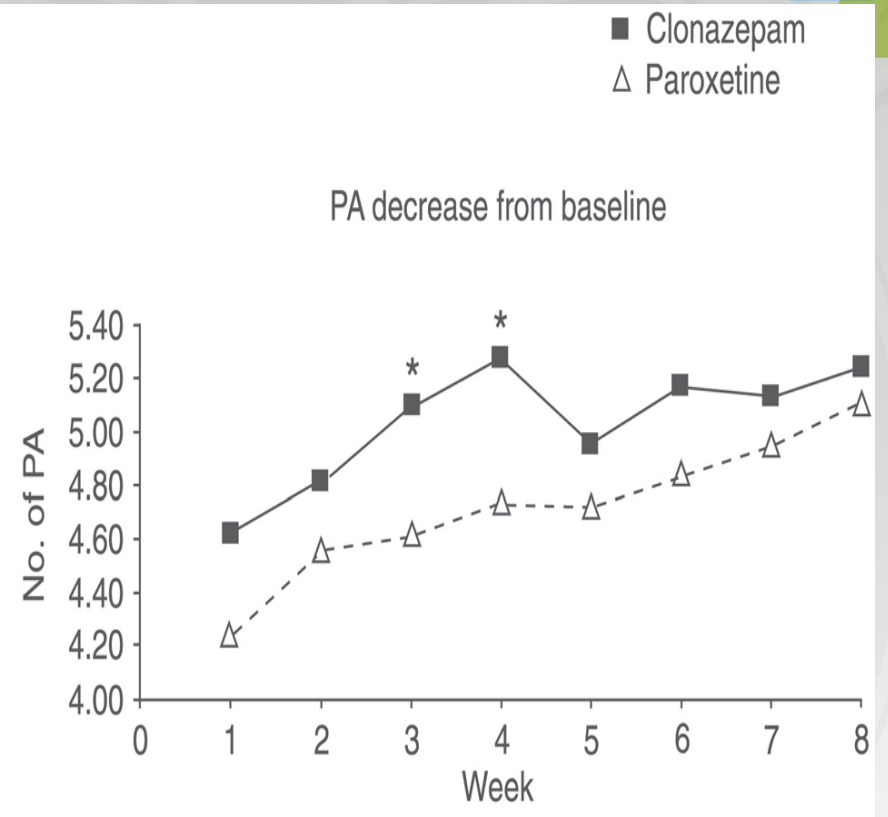
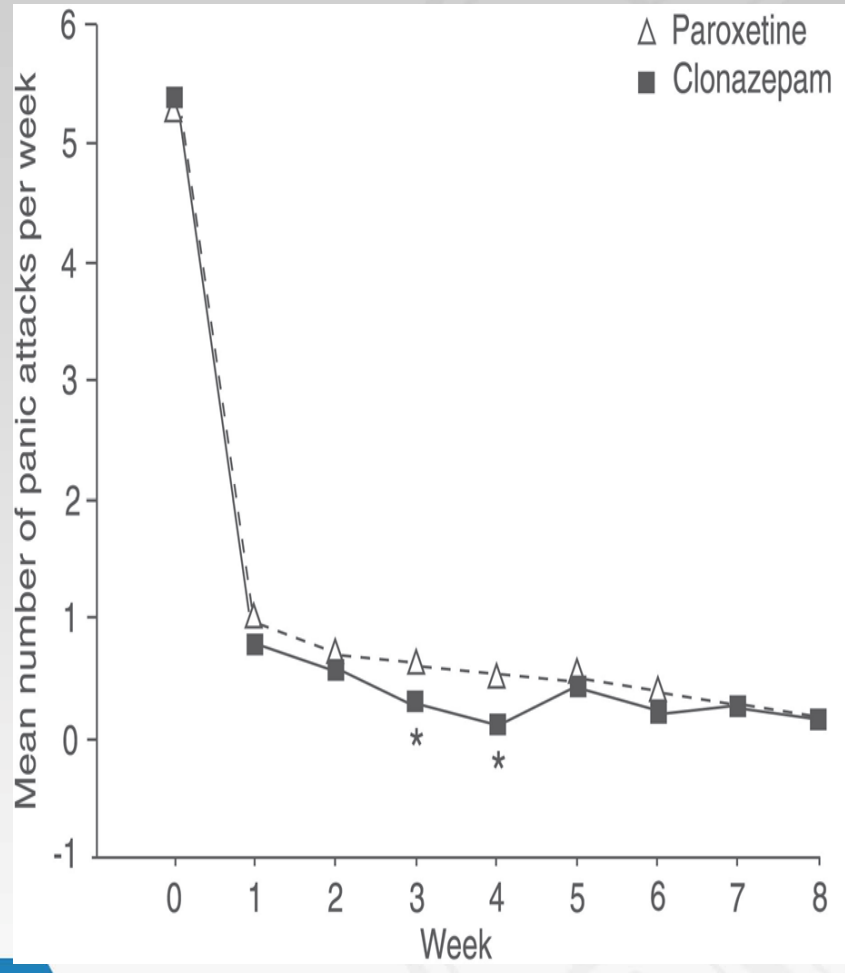
Tolerability

- Drowsiness parox 81% clonaz 57%
- Sex dys parox 70% clonaz 11%
- N/V parox 61% clonaz 0%
- Mem/conc parox 40% clonaz 24%

- Completed 8 wks
 - ❖ parox 96.5% clonaz 98.4%



Nardi AE. Braz J Med Biol Res. 2011.



Nardi AE. Braz J Med Biol Res. 2011.

Guideline recommendations

GAD



- British Association of Psychopharmacology (2014)
 - Acute phase
 - Start SSRIs, TCAs and add BZD if necessary
 - Prophylaxis
 - SSRIs, SNRIs, buspirone, pregabalin
- NICE (2011)
 - SSRIs preferably sertraline. If ineffective offer a different SSRI or an SNRI.
 - Consider pregabalin if the person cannot tolerate SSRI/SNRI.
 - Do not offer BZD except for short term during crises.



Guideline recommendations

GAD



- Canadian Psychiatric Association (2014)
 - First Line
 - SSRIs and SNRIs, pregabalin.
 - Second line
 - Benzodiazepines, buspirone, TCAs, bupropion XL.
 - Benzodiazepines should be used only for short term.



Guideline recommendations

Panic Disorder



- British Association for Psychopharmacology (2014)
 - ❖ Acute phase treatment
 - SSRIs, TCAs, venlafaxine
 - With BZDs if necessary
 - ❖ Prophylaxis
 - SSRIs, TCAs
- NICE (2011)
 - ❖ Antidepressants should be the only pharmacologic intervention in the long term management.
 - Duration of therapy at least 6 months
 - ❖ TCAs if multiple SSRIs fail
 - ❖ BZDs are associated with a less good outcome in the long term and are not recommended



Guideline recommendations Panic Disorder



- American Psychiatric Association (2008)
 - SSRIs and SNRIs
 - TCAs
 - BZDs for the first 4-6 weeks of treatment only.
- Canadian Psychiatric Association (2014)
 - First line SSRIs and venlafaxine
 - Second line mirtazapine, TCAs and BZDs
 - BZDs are recommended for short term treatment



BZD risks

- Abuse seems to be related to a combination of all α receptors, specifically $\alpha 1$
- BZDs also agonizes opiate receptors
 - ❖ Primarily κ receptors
 - Midazolam may have additional δ receptor agonism.
- Enhances feeling euphoria with opiates.

Ator NA. CNS Spectrums. 2005.
Cox RF. Anesth Analg. 2001.

BZD risks



ED visits

- Increase in BZD related ED visits from 2008-2011 by 56%.
 - ❖ Many involving EtOH.
- Opiate and BZD risks.
 - ❖ 50% of OD involve opiate and BZD.
 - ❖ Heroin users report up to 80% of their non fatal ODs involved a BZD.
 - ❖ BZDs are involved in 50-80% of methadone related fatal ODs.
 - ❖ 30% of fatal opiate ODs had a concomitant BZD in 2010.
 - 77% of fatal BZD ODs also included opiates.



SAMHSA DAWN report. 12/18/2014.

Jones JD. Drug Alc Dep. 2012. Jones CM. JAMA.2013.



Bluelight.org

- I took 30mg hydrocodone and need help falling asleep. Took 2mg etizolam 10 minutes ago and plan on feeling good for a little while then passing out. Is this combination really that bad?

www.bluelight.org/vb/threads. 25-04-2012.





Bluelight.org - responses

- I died for almost a minute on the combination.
- I really blacked out and woke up from a dream realizing I just smashed my car.
- I did 8mg of Xanax and 40mg Opana no problem. I did 13mg of Xanax and 40mg Opana and woke up with a doctor staring down at me amazed I was still alive.
- I have overdosed and actually died due to benzos and opiates.





Bluelight.org - responses

- If you know your limits it can go fine.
- If you are tolerant to opiates and benzos, and dose accordingly, you are not guaranteed death. Plenty of us combine the two.
- Even now I don't leave home without washing 4mg of clonazepam with methadone syrup.
- I usually find the heroin in the UK so weak I won't bother getting heroin unless I got some benzos.



BZD risks

- Healthcare costs related to accidents increase post BZD initiation compared to alternative treatment pts.
- Motor Veh. Acc.
 - ❖ 60-80% increase in risk.
 - Coingestion with EtOH increases risk by %770
 - ❖ Antidepressants that are not sedating have no increased risk.
 - Sedating antidepressants increase risk in elderly.

Berger A. BMC Psychiatry. 2012.
Smink BE. CNS Drugs. 2010.
Dassanayake T. Drug Safety. 2011.

BZD risks

- Withdrawal
 - ❖ Should not underestimate difficulty of tapering BZDs.
 - Insomnia, rebound anxiety
 - Up to 5 week taper, 43% had worse anx. than their baseline
 - Seizure
- Disinhibition
 - ❖ In those predisposed to impulsive outbursts.
 - ❖ Maybe suicidal acts.
- May impact ability to benefit from psychotherapy.

Schweizer E. Am J Psychiatry. 1993.
Baldwin DS. J Psychopharmacology. 2013.

BZD risks

- Cognitive impairment
 - ❖ Impaired functioning in all domains with long term use and reaction times.
 - improvement occurs within 1 month of cessation but not full recovery.
 - ❖ Duration of use positively correlates with Alzheimer's diagnosis.
 - ❖ Long term use is considered over 180 days continuous.

Baldwin DS. J Psychopharmacology. 2013. Stewart SA. J Clin Psychiatry. 2005.
Barker MJ. Arch Clin Neuropsychology. 2004. Bellioti de Gage S. BMJ. 2014.
Puustinen J. Eur J Pharmacol. 2014.

SSRI/SNRI risks



- Suicidal events and thinking
 - ❖ Risk is decreased in adults >24 compared to placebo.
 - ❖ Self harm is slightly increased, suicide and suicidal thinking is decreased.
- Bleeding
 - ❖ Small increase in upper GI bleed.
 - ❖ NNT for one event is 3177.
- QTc
 - ❖ All SSRIs combined averaged to increase 6msec over placebo.
 - ❖ Citalopram clearly worse than others.
 - fluox, sert, fluvox, parox about the same.

Gunnell D. BMJ. 2005. Lam RW. J Affective Disorders. 2007.
Andrade C. J Clin Psychiatry. 2010. Anglin R. Am J of Gastroenterology. 2014.
Beach SR. J Clin Psychiatry. 2014. Funk KA. Ann Pharmacotherapy. 2013.





GAD and PD comorbidity of depression

- At least half of GAD patients will develop MDD.
- 30-60% of Panic patients will develop MDD.
- Comorbidity correlates with:
 - ❖ less robust response
 - ❖ increased suicide.
- Up to 80% of patients with MDD have an anxiety disorder.

Moffitt T. JAMA Psychiatry. 2007.

Baldwin DS. J Psychopharmacology. 2014.

Katzmann MA. BMC Psychiatry. 2014.



treatment effect on depression

- BZDs have shown no benefit as an antidepressant.
 - ❖ Although small benefits are seen in patients with significant anxiety impairment.
- Antidepressants.....do show benefit.
- VA registry showed: 36% of depressed pts filled BZD rx.
 - ❖ 94% (of the 36%) were also prescribed antidepressants.
 - ❖ Regarding BZD use:
 - 78% was for > 90d (or 28% of all depressed pts)
 - 61% was for >180d (or 22% of all depressed pts)
 - Higher medical costs in BZD group

Baldwin DS. J Clin Psychopharm. 2013.

Baldwin DS. BAP Treatment Guideline. J Clin Psychopharm. 2014.

Valenstein M. Am J Psychiatry. 2004. Katzmann MA. BMC Psychiatry. 2014.

N. America BZD utilization



- 5.2% adults filled at least one BZD rx in 2008
 - ❖ Women 2x more likely to have a BZD Rx.
 - ❖ Approximately 3% use BZD long term (>120d).
- Any BZD use increases with increased age groups.
 - ❖ 2.6% (18-35 years)
 - ❖ 5.4% (36-50 years)
 - ❖ 7.4% (51-64 years)
 - ❖ 8.7% (65-80 years)
- Long term BZD use increases with age groups
 - 14.7% (18-35 years), 31.4% (65-80 years). (% of BZD users)
- Long term users increased from 1996-2006 in Brit Col. (100d/yr)
 - ❖ Has remained stable over last 20 years in other countries including US.



Olfson M. JAMA Psychiatry. 2015.
Cunningham CM. Health Policy. 2010.

summary

- Benzodiazepines may be prescribed safely in the short term
 - ❖ patients whose quality of life is significantly affected by distressing anxiety symptoms or troublesome insomnia. A minimum of 3 SSRI/SNRIs should be used.
 - ❖ Benzodiazepines can be used longer term, if...
 - the patient periodically attempts to slowly reduce the dosage at regular intervals and tries to stop altogether when or if possible.

Baldwin DS. J of Psychopharmacology. 2013.



Local data

- 2015 Jan – Aug (n=12,000)
- Clients with chronic BZD treatment (90 out of last 120d).
 - Only 51% had a SSRI or SNRI rx.
 - This includes the newer agents of milnacipran, vortioxetine and vilazodone.
 - Or...nearly half of those using BZDs regularly are not taking a medication recommended by experts.
 - Assuming that this 49% are being treated for an anxiety disorder.



Next step

Target: primary care is the greatest prescriber of long term BZDs.

- Guideline education.
- Patient profile reminder.
 - ❖ One reminder or monthly x4 with strategy is beneficial.

Patient education:

- ❖ Slow taper to avoid physical withdrawal and rebound.
 - As well as eliminating psychological dependence.
- ❖ Physician and/or pharmacist can be educator.
 - 27% d/c'd BZD interven. grp v 5% in UC grp.*

Cormack MA. Br J of Gen Practice. 1994.

*Tannenbaum C. JAMA Intern Med. 2014.





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