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Commentary: Benzodiazepine (BZD) and Related BZD-Receptor Agonists: Basic Science Reasons to Limit to Four Weeks or Less

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Abstract

Benzodiazepines and related benzodiazepine-receptor agonists such as the pyrazolopyrimidinezaleplon; the imidazopyridine zolpidem; and the cyclopyrroloneszopiclone and eszopiclone, are among the most widely prescribed drugs, and for a variety of conditions. Surprisingly: 1) there are only a few conditions for which there is a good evidence basis, 2) efficacy has only been well demonstrated for short-term use (*i.e.*, less than 4 weeks), and 3) much less is known about the basic science of these drugs than is widely believed. We suggest that the use of these drugs beyond four or less weeks exceeds the available knowledge base, so best-practice use suggests that the prescribing of these drugs for most patients should be limited to only short-term use until more is known about the basic pharmacology of their actions in the brain and in the periphery.

Keywords

Benzodiazepine (BZD), BZD-Receptor Agonist, Evidence-Based, Short-Term Use

1. Introduction

Benzodiazepine (BZD) and related BZD-receptor agonists are consistently among the top most-prescribed drugs. A recent list of the top 200 most-prescribed drugs in the United States lists alprazolam at #23, zolpidem at #46, lorazepam at #55, and diazepam at #91 [1]. This places the category as a whole close to the

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top. Prior to the introduction of selective serotonin reuptake inhibitors (SSRIs), the use of BZDs was even more widespread. Current use is primarily for treatment of anxiety, insomnia, or certain seizures [2] [3] [4] [5]. Some uses, such as for muscle relaxation or pain relief, among others, have little evidence-basis for support, and even have evidence against their use. Concurrent use with opioids is a known contraindication [6]. However, as stated in the comprehensive recent review by Guina and Merrill, even for the conditions that BZDs have demonstrated efficacy, *they are only recommended for short-term use* (less than 2 - 4 weeks) [7]. Nevertheless, BZDs continue to be used in ways not supported by the literature [7].

Part of the problem appears to stem from unjustified exaggerated attitudes regarding benzodiazepine efficacy, a perceived lack of alternative treatment options, perception of patient expectations and the doctor-patient relationship (drugs of "convenience"), and an underestimation of adverse effects and problems with withdrawal (acute or prolonged) [8]. We point out another consideration to add to rationale for limiting BZD use to less than 2 - 4 weeks (except for special cases, such as failing multiple evidence-based 1st, and perhaps 2nd-line treatments): a surprising inadequate knowledge-base about the basic pharmacology of BZDs.

2. The Trajectory of Benzodiazepines in Therapy

The benzodiazepines ushered in a metamorphosis in the treatment of—and even the thinking about—mental health: namely, that there are underlying biochemical causes or correlates. The BZDs even stimulated basic research into the highly-refined picture of the $GABA_A$ receptor that we have today. And displacement of the then current therapy (primarily barbiturates) has benefited countless patients.

Indeed, the BZDs were originally thought to be a medical miracle: efficacious, safe, and devoid of withdrawal problems during discontinuation. [9] Why then have the BZDs and related BZD receptor agonists such as the so-called "Z" and other drugs, with the best of original intentions (albeit also with some questionable marketing practices), become "Our Other Prescription Drug Problem"? [10]

3. Benzodiazepine Pharmacology

Benzodiazepines are defined by the specific arrangement of a benzene ring plus a diazepine ring. The so-called "Z"-drugs lack the distinctive BZD chemical structure (**Figure 1**), but act in the same way as do BZDs. Since they have similar pharmacology, they are considered here together.

Benzodiazepines produce their effects in the brain by agonist action at BZD-Rs. The brain contains high-affinity binding sites for benzodiazepine agents, which bind to these sites in a way that is stereospecific and saturable (**Figure 2**) [11]. This action allosterically potentiates the inhibitory effects of gamma(γ)-aminobutyric acid (GABA), which is a neurotransmitter that

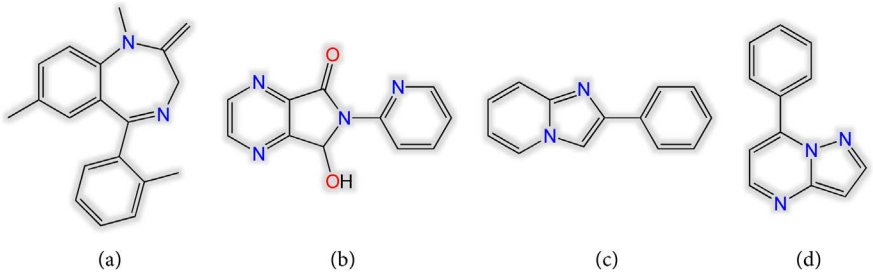

Figure 1. Structural template of BZDs (a) and some non-BZD BZD-R agonists: cyclopyrrolones (e.g., eszopiclone) (b); imidazopyridines (e.g., zolpidem) (c); and pyrazolopyrimidines (e.g., zaleplon) (d).

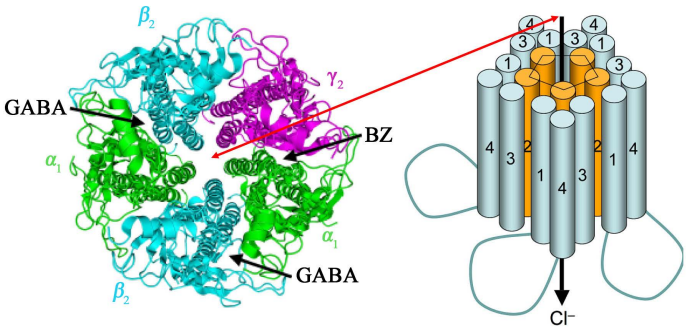

Figure 2. The $GABA_A$ receptor and BZD site. From https://commons.wikimedia.org/wiki/File:NAchR_2BG9.png; https://commons.wikimedia.org/wiki/File:GABAA-receptor-pro-tein-example.png; and https://commons.wikimedia.org/wiki/File:Cell_GABA_Receptor.png.

mediates inhibitory transmissions at most brain neurons [12] [13] [14]. The $GABA_A$ receptor is an ionotropic type receptor, which means that it is a ligand-gatedion channel. There are multiple subtypes of the $GABA_A$ receptor subtype [15]. Activation by an endogenous agonist (*i.e.*, GABA), exogenous agonist, or positive allosteric modulator acting as agonist at BZD receptors (e.g., benzodiazepines or "Z"-drugs) results in an increase in Cl^- influx as the mechanism of signal transduction. Most $GABA_A$ receptors in the brain consist of five subunits, which are designated α, β, and γ [15]. There are a large number of possible subunit combinations since there are at least six different α-subunits, four different β-subunits, and three different γ-subunits. This diversity results in $GABA_A$ receptors with different and distinct electrophysiological and pharmacological characteristics.

4. Problem: What We Know

Since introduction of drugs with selective mechanisms (e.g., SSRIs), there is little evidence-basis for continued use of BZDs for many conditions, and certainly not for use longer than 4 weeks (or less) [7]. As just one example, a recent meta-analysis found that BZDs did not significantly decrease time of sleep onset compared to placebo (**Figure 3**) [16].

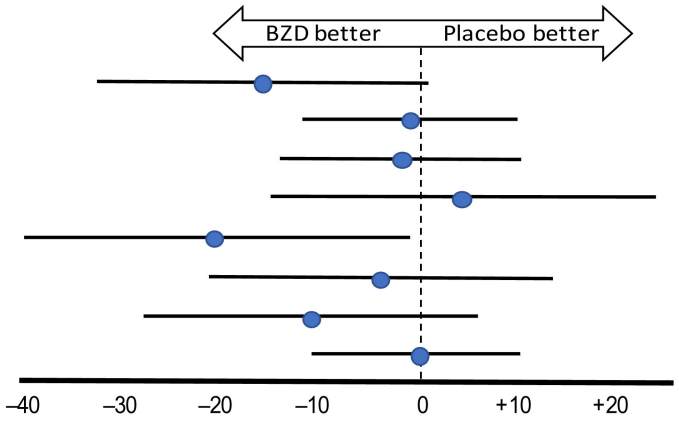

Figure 3. Mean difference in sleep latency, BZDs vs. placebo (1 - 7 day treatment). From [16].

5. Bigger Problem: What We Don't Know

There are very few drug classes whose mechanism of action seems definitive. The anxiolytic action of BZDs is an exception. It has been a long-held tenet of pharmacotherapy that BZDs produce their anxiolytic effects by interacting with $GABA_A$ receptors in the brain [17] [18] [19] [20]. This has been accepted as dogma through the years and, unfortunately, has in retrospect tended to deemphasize impetus for additional investigation.

The following are just some of the basic-science findings that suggest that long-term prescribing of BZDs takes the prescriber and the patient into uncharted territory:

- With long-term exposure to BZDs, $GABA_A$ receptors change. So do BZD receptors. For example, down-regulation of BZD receptors and subunits of $GABA_A$ receptors (and the receptor mRNA) occur with a concomitant decrease in the responsiveness of $GABA_A$ receptors (measured a selectrophy-siological response, transmembrane GABA-gated Cl^-flux, and functional coupling). Thus, a patient's $GABA_A$ and BZD receptors after more than a few weeks of BZD exposure are not the same as at start of therapy [6] [8] [17]-[24].
- There is a surprising paucity of information about the receptor binding profile of many of the BZDs at off-target sites. For most other drugs, extensive receptor profiling is easily accessible. Radioligand binding data are available for BZDs at BZD receptors, but not at other receptors.
- BZDs have little-known or underappreciated actions at receptors other than their well-known $GABA_A$ receptor action e.g., BZDs potentiate adenosine A_{2A} receptor-mediated effects, allosterically modulate α_1-adrenoceptor signaling by inhibiting phosphodiesterase-4, and possibly have agonist action at oxytocin receptors [25] [26] [27] [28] [29].
- Little-known, and even less-understood, are peripheral BZD receptors (PBR) (**Figure 4**). They are located in abundance in the peripherally, critically, on mitochondria and immune cells [30] [31].

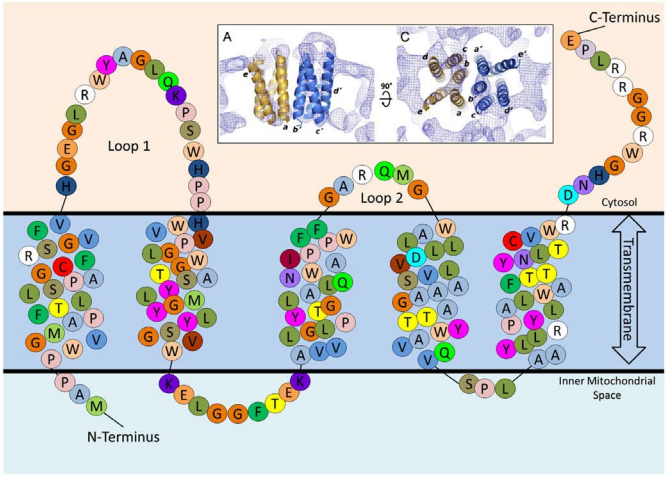

Figure 4. Schematic of a topological model of the human peripheral PBR. Cytosolic loop 1 and loop 2 are the binding sites for benzodiazepines. From Austin *et al.* (2013) [34] with permission.

- Control-system compensatory mechanisms, such as hysteresis might alter thenormal development of tolerance or physical dependence, or withdrawal [32].
- Enigmatic protracted withdrawal symptoms occur in some patients, possibly related to peripheral BZD receptors or to translational or epigenetic changes [33].

6. Conclusions

It is not the purpose of the present Commentary to review all of the basic science findings that have been reported in the intervening years, but to point out that the implications of these findings to a great extent have not been factored into clinical prescribing practice. Some might not be clinically-relevant, others might have profound implications. The message of this commentary is that no one really knows. It is thus a call for action or perhaps in this case a call for inaction.

Until the new physiological phenomena and receptors are better understood, and there are validated clinical data, supported by basic-science, and evidence-based guidance, the prescribing of BZDs and other BZD-receptor agonists should not exceed the evidence, that is, not be prescribed for more than 4 weeks, and possibly shorter.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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