

## Benzodiazepines

### Overview

Commonly called 'Benzos', *benzodiazepines*, is a group of synthetic chemicals that act as depressants on the central nervous system. They act as, and are sub divided into, *anxiolytics*, *hypnotics*, *sedatives* and *anti-convulsants*. They also work as muscle-relaxants.

These drugs have at times been heavily prescribed as they cover a wide range of symptomatic conditions and have become available on the illicit internet market. While benzos usually come in tablet or capsule form, there are various brands, sizes, shapes and colours. They are usually taken orally, although some people do inject (an injectable preparation is produced almost exclusively for inpatient pre/post-operative sedation). The 1980s and early 90s saw the emergence of a massive problem, mainly in Scotland, around the injection *temazepam* (jellies, eggs, temazies). Other commonly used benzodiazepines include diazepam (Valium), flunitrazepam (Rohypnol, 'roohies' or 'roofies'), alprazolam (Xanax) and nitrazepam (Mogadon, 'moggies'). There are numerous others - see PDF for detailed information on all the above and the newer 'non addictive' benzo-type sedatives.

These drugs, once known as minor tranquillizers, generally make the user feel calm and sleepy; their effect is enhanced when combined with alcohol or any depressant. They are regarded as a highly effective short-term medication; however, many patients who were originally prescribed stronger sedatives were transferred to benzos and effectively left on them for decades. The current 'anti- Benzo' orientation of many PCT's and younger doctors has caused genuine distress and hardship for this ageing population (see PDF for case histories) whose long term usage reached the point where cessation may be more problematic than maintenance. Users also can develop tolerance to their effects, and dependent users can go on to take enormous daily doses. Withdrawal then becomes a dangerous process which can lead to fits, convulsions, prolonged dysphoria and depression, and changes in dose regimes should be carried out only under competent medical supervision.

### Chemistry

Benzodiazepines produce a range of effects from depressing to stimulating the central nervous system via modulating the GABA<sub>A</sub> receptor, the most prevalent inhibitory receptor within the brain. The subset of GABA<sub>A</sub> receptors which also bind benzodiazepines are referred to as benzodiazepine receptors (BzR). The GABA<sub>A</sub> receptor is composed of five subunits, most commonly two  $\alpha$ 's, two  $\beta$ 's, and one  $\gamma$  ( $\alpha_2\beta_2\gamma$ ). Furthermore for each subunit, multiple subtypes exist ( $\alpha_{1-6}$ ,  $\beta_{1-3}$ , and  $\gamma_{1-3}$ ). GABA<sub>A</sub> receptors which are made up of different combinations of subunit subtypes have different properties, different distributions within the brain, and different activities relative to pharmacological and clinical effects.

Benzodiazepines bind at the interface of the  $\alpha$  and  $\gamma$  subunits on the GABA<sub>A</sub> receptor. Benzodiazepine binding also requires that alpha subunits contain a histidine amino acid residue, (*i.e.*,  $\alpha_1$ ,  $\alpha_2$ ,  $\alpha_3$  and  $\alpha_5$  containing GABA<sub>A</sub> receptors). For this reason, benzodiazepines show no affinity for GABA<sub>A</sub> receptors containing  $\alpha_4$  and  $\alpha_6$  subunits, which contain an arginine instead of a histidine residue. Other sites on the GABA<sub>A</sub> receptor also bind neurosteroids, barbiturates and certain anesthetics.

Once bound to the BzR, the benzodiazepine ligand locks the BzR into a conformation in which it has a much higher affinity for the GABA neurotransmitter than otherwise. This increases the frequency of opening of the associated chloride ion channel and hyperpolarizing the membrane of the associated neuron. This potentiates the inhibitory effect of the available GABA, leading to sedative and anxiolytic effects. As mentioned above, different benzodiazepines can have different affinities for BzRs made up of different collections of subunits. For instance, benzodiazepines with high activity at the  $\alpha_1$  are associated with sedation, whereas those with higher affinity for GABA<sub>A</sub> receptors containing  $\alpha_2$  and/or  $\alpha_3$  subunits have good anti-anxiety activity. Benzodiazepines also bind to glial cell membranes.

Some benzodiazepines are full BzR agonists, producing anxiolytic and sedating properties. Compounds that, in the absence of agonist, have no apparent activity but that competitively inhibit the binding of agonists to the receptor are called BzR antagonists. Ligands that decrease GABA function are termed benzodiazepine receptor inverse agonists. Full inverse agonists have potent convulsant activities.

Some compounds lie somewhere between being full agonists and neutral antagonists, and are termed either partial agonists or partial antagonists. There has been interest in partial agonists for the BzR, with evidence that complete tolerance may not occur with chronic use, with partial agonists demonstrating continued anxiolytic properties with reduced sedation, dependence, and withdrawal problems.

However the anticonvulsant properties of benzodiazepines may be in part or entirely due to binding to voltage-dependent sodium channels rather than benzodiazepine receptors. Sustained repetitive firing seems to be limited by benzodiazepines effect of slowing recovery of sodium channels from inactivation.

Benzodiazepine receptors also appear in a number of non nervous-system tissues and are mainly of the peripheral benzodiazepine receptor (PBRs) type. These peripheral benzodiazepine receptors are not coupled (or "attached") to GABA<sub>A</sub> receptors. These are found in various tissues such as heart, liver, adrenal, and testis, as well as hemopoietic and lymphatic cells.

Benzodiazepines are usually divided into three classes; these are determined by the duration of action of the three groupings. Short-acting compounds have a half-life of 12 hours; intermediate compounds have a half-life of 12-24 hours, and long acting compounds which have a half-life of over 24 hours. The first group have few after-effects if taken before sleep, but rebound insomnia may occur and daytime anxiety; rebound insomnia is also more common upon withdrawal of the short-acting drug. The intermediate group are more likely to produce after-effects in the first part of the following day. In general, the longer the action, the greater the effects of drowsiness.

## History

The first benzo was produced in 1954 by Austrian scientist Leo Sternbach, and was marketed by Hoffman La Roche as *Librium* in 1960. *Valium* followed 3 years later. Numerous other benzodiazepines followed- another 25 within 20 years, but the discovery of these first tranquillizers was heralded as the dawn of an age without anxiety. Librium was named after Equilibrium, a state of balanced calm. When the UK press heard of a trial in which Librium

was used on animals at San Diego zoo, one newspaper headlines the story thus: “The Drug That Tames Tigers- What will it do for Nervous Women?”

It was believed that the drugs could alleviate anxiety without any corresponding loss of mental clarity. Hoffman LaRoche became the largest pharmaceutical company in the world on the back of sales of Librium and Valium. By the 1980s, benzos were the most widely prescribed drugs in the UK; over 4% of all prescriptions were for diazepam (Valium).

### Use and culture

They are used for the treatment of anxiety, insomnia, convulsions, alcohol withdrawal symptoms, muscular disorders, as pre-meds before surgery and in veterinary medicine. Side effects can include drowsiness, dizziness, blurred vision, confusion, depression and more.

Many people today use benzos illicitly as part of a pattern of poly-drug use, assisting and easing the comedown from cocaine or crack cocaine, for example, or after using amphetamines, when people often feel anxious and stressed.

Long-term use can lead to dependence - these are addictive drugs. Withdrawal can be dangerous as it may include fits, convulsions, prolonged dysphoria and depression; it should be carefully managed by means of transference onto diazepam, which has the longest half-life of all the benzodiazepines, and a slow reduction programme should be undertaken under medical supervision. Moreover, it is important for the process to be overseen by a physician with a good understanding—and preferably practical experience—of the treatment of benzodiazepine withdrawal syndrome. As mentioned in the introduction, benzos have recently been the object of changes in prescribing practices; whereas they were previously viewed as almost entirely benign and liberally prescribed, there is now a strong movement toward removing patients from their use. If this is done insensitively and without the active and willing cooperation of the patient in therapeutic partnership, the consequences of withdrawal can be worse than allowing the patient to be maintained on the drug.

### Casework from the Release drugs helpline

At the Release drugs helpline, a sizeable percentage of the time dedicated to helpline clients has recently been orientated specifically toward clients maintained on long-term benzodiazepines (and barbiturates). We have dealt with a number of elderly patients who seem to be stranded on drugs that were initiated by NHS prescribers over 20 (and in some cases over 35) years ago. These patients are with doctors who are now being told, probably as a result of PCT directives to stop long-term maintenance treatment with these drugs, to limit all benzodiazepine prescribing to 14 days maximum.

In all of these cases the patients are beyond retirement age and entirely lucid, and will have experienced a significant degree of neural adaptation over the years. Benzodiazepines have, in all probability, become an indispensable facet of their individual and social functioning. Forcing them into detoxification either against their wishes or on accelerated regimen seems to us to be cruel and unnecessary. We have consulted on this question with both addiction specialist clinicians and general practitioners with a proficiency in psychopharmacology. They are in agreement with the Release drugs team that, while every case must be looked at individually, there is an unrealistic degree of wish-fulfilment about GP practices offering

‘detoxes’ by increment without fully considering the impact that their decisions are having on people who find themselves marginalised—and even disbelieved and ridiculed—when they complain that they cannot cope with the side effects of reduction or detox.

We will continue to try to make practitioners aware of the complexity of this area of practice. Some of these clients are people who may once have been labelled iatrogenic addicts—although addict is a term that has not often been associated with the elderly rural middle classes. The undue distress caused by these insensitive and coercive practices, whatever the intentions underlying them, runs counter to a medical ethics centred on the principle “First, Do No Harm” and to the inclusive spirit of the National Health Service.