The Effect of Benzodiazepines and Non-Benzodiazepines on Ingestive Behavior

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Abstract

The aim of the present review was to examine current research centering on benzodiazepines and non-benzodiazepines and their effect on ingestive behavior. For years, benzodiazepines have been used to treat anxiety and occasionally seizure disorders. However, every benzodiazepine that has been produced thus far shares a common side effect of hyperphagia, or over consumption of palatable stimuli. Benzodiazepines and bind to GABA-A receptors in the brain. Due to the location of these receptors, it is believed that the receptors are important to the enhanced palatability seen with benzodiazepines. As years have passed, more has become known about each of these drugs, and more selective options have been produced in order to eliminate some of the negative side effects. However, hyperphagia has persisted throughout the many attempts to eliminate this side effect.

Opioids are not actually part of the benzodiazepine family. They have commonly been studied along with benzodiazepines, for opioids create hyperphagic side effects similar to those of benzodiazepines, even though the two types of drugs are very different. Some research has compared the similarities of benzodiazepines and opioids, however it had been found that both drugs bind to different receptors in the brain with benzodiazepines binding to GABA-A receptors and opioids binding to mu and kappa receptors. The two drugs also treat different symptoms with opioids commonly used as an analgesic and benzodiazepines are used as anti-anxiety and anti-seizure medications.

It is the purpose of this review to examine benzodiazepines such as chlordiazepoxide, midazolam, and bretazenil and view the different effects when comparing to non-benzodiazepines such as abecarnil and opioids.
Introduction

Benzodiazepines and non-benzodiazepines, drugs that treat similar symptoms but do not possess benzodiazepine side effects, are commonly prescribed drugs in the United States in treatment of anxiety, sleep deprivation and muscle spasms. Benzodiazepines are similar to non-benzodiazepines in that they both retain anti-anxiety and anti-convulsant properties, but the two drugs provide drastically different effects on ingestive behavior. Many benzodiazepine treatments have been found to elevate the level of food consumption of test subjects. Cooper and Estall (1985) have found that elevated food consumption is able to be generalized across many mammalian species regardless of food deprivation. An early explanation of weight gain was that the sedative side-effects of benzodiazepine treatments interfere with some behavioral acts such as moving from one location to another, and because the animals are more lethargic and do not move as much, the animals manage to consume more food (Cooper & Estall, 1985).

Benzodiazepines modulate affective taste responses to food stimuli more than perceived physiological states of repletion or depletion (Pittman et al, 2012). Essentially, benzodiazepines have been found to alter taste responses to food more than is physiologically necessary for survival. Contrary to classic benzodiazepines, when non-benzodiazepines and anti-convulsants are administered, the opposite effects are found where the subject’s overall food consumption decreases. Benzodiazepines and similar compounds bind to highly specialized sites within the body and central nervous system.

It has been suggested that benzodiazepines may act on multiple neural levels of the brain only to affect a single psychological or behavioral system. GABA is the main inhibitory neurotransmitter in the mammalian central nervous system (CNS), and a benzodiazepine works by facilitating GABAergic transmission by facilitating endogenous Cl⁻ ion channels (Richards &
Möhler, 1984). Binding sites can be found throughout the brain, but it has been suggested by Berridge (1988) that the forebrain contains a higher amount of binding sites, with the mid and hind brain containing some binding sites in higher concentrations as well, and especially around the fourth ventricle (Berridge, 1988). Binding sites are important because the receptor contains pharmacologically relevant recognition sites of traditional benzodiazepines, while peripheral binding sites show a high affinity for non-benzodiazepines (Richards & Möhler, 1984). Binding sites for the benzodiazepines can be classified into two types: central and peripheral. Central binding sites pertain to the binding sites in the CNS while peripheral binding sites mostly pertain to the peripheral organs of the body. The central binding sites are believed to be located in areas of synaptic contact in the CNS, while peripheral binding has the ability to occur mainly in localized to glia cells (Richards & Möhler, 1984).

Each benzodiazepine will fall into one of three groups of ligands that will bind into either the central or peripheral sites. The three groups of ligands are receptor agonists, inverse agonists, and antagonists. The receptor agonists increase the coupling between GABA and a chloride channel, and are seen as the typical benzodiazepines such as midazolam or chlordiazepoxide. Antagonists prevent access to the benzodiazepine receptor for agonists. Agonists perform this action because of competitive inhibition and blocking. The agonist competes with naturally occurring substances in the brain so that the agonist can bind first. Once the agonist is bound, other substances are not able to bind to the receptor and thus the antagonist has the ability to perform its specific task. Reverse agonists are highly selective for benzodiazepine receptors. These highly selective receptors will not be activated unless a benzodiazepine or similar compound like a reverse agonist binds in the receptor site. Inverse agonists decrease coupling between GABA and a chloride channel. They do not induce a hyperphagia like that found in
classical benzodiazepines, but instead decrease food intake. Inverse agonists are typically esters or amides (Richards & Möhler, 1984). Inverse agonists generally produce opposite effects found to that of classic benzodiazepine agonists (Cooper et al, 1987). For the purpose of this review, receptor agonists and inverse agonists will be more heavily investigated. Receptor agonists have been found to increase behavioral responses to tastants (as reported in Pittman et al, 2012), and inverse agonists have been found to produce opposite hyperphagic effects to that of the classic benzodiazepine.

Chlordiazepoxide

Chlordiazepoxide (CDP) was produced in the 1970’s, is the oldest and was the first synthesized benzodiazepine. CDP has less selective effects than newer benzodiazepines. CDP is one of the most commonly studied benzodiazepines when looking at taste mediated hyperphagia (Pittman et al., 2012). Many studies have shown that effects of CDP make palatable stimuli more attractive, and some studies report similar findings for generally non-palatable substances such as quinine. CDP has shown an increase of the amount of time at food trays in anticipation of food reinforcement. It facilitates approach responses when food pellets are goal objects and delivery is anticipated (Cooper & Estall, 1985). As Cooper & Estall (1985) stated, the food is seen as a reward and is highly desirable to the subject. With the influences of the drugs, highly palatable substances are consumed in larger quantities and at a higher rate than when the subject is not under drug influences. These behaviors of high rates of consumption have been found across numerous studies but most of the studies do not find increase in consumption with non palatable or aversive stimuli. CDP’s effects can be subdivided into two categories: the duration of feeding responses, and rates of food intake while feeding is occurring (Cooper & Francis, 1980).
The duration of feeding responses simply refers to the length of time a subject consumes a food substance that has been presented. Feeding responses are commonly used to determine palatability of substances based on how much of the food the subject consumes. Cooper and Francis (1980) suggest that within a short duration feeding test, CDP was found to prolong the duration of the feeding of rat chow and other foodstuffs. The rate of feeding refers to the amount of licks of taste solutions in a given period of time. Pittman et al. (2012) found results similar to that of Cooper and Francis (1980) where in addition to prolonging the duration of feeding, CDP reduced the mean pause between licks. This led to larger meals compared to control subjects because the test subjects were able to consume more food due to fewer pauses between licks (Pittman et al, 2012). The question then persists of whether CDP is actually enhancing the tastes of palatable stimuli and causing more food consumption, or is the CDP reacting with structures in the brain to produce such hyperphagic effects with palatable stimuli.

A combination of both brain areas and drug effects has an influence on CDP’s hyperphagic effects with palatable stimuli. Receptors for benzodiazepines can be found in all areas of the brain, but some areas have higher concentrations such as areas around the fourth ventricle and mid brain. Berridge (1988) found that the mid and hind brain clearly retain the capacity to increase positive taste-elicited ingestive responses with CDP when isolated from the forebrain. Therefore, it can be implied that GABA receptors are required for palatability modulation and minimum neural circuits to translate receptor activation. Berridge explains here that because the number and availability of benzodiazepine receptors in the mid and hind brain, GABA is an important neurotransmitter in CDP’s ability to produce hyperphagic effects of palatable stimuli. Berridge in the same study suggests that palatability of CDP may be due to spontaneous intake. This would require forebrain structures in addition to the midbrain and hind
brain structures previously mentioned. Pittman et al. (2012) suggested that independent binding sites of CDP might exist. It was suggested that some areas of the brain control the hyperphagia that is induced with CDP, while other binding sites would control oromotor coordination. Each study suggests slightly different hypotheses that hold credibility. It is currently believed that the parabrachial nucleus (PBN) and the fourth ventricle of the brainstem are brain structures that control much of the hyperphagia associated with CDP. These sections are believed to be highly involved with the hyperphagia associated with CDP because both areas are important in the taste projection system (Cooper & Ridley, 2005).

It was found in Pittman et al. (2012) that CDP significantly reduced the mean pauses between licks and increased the total meal size, but these were not true with unpalatable substances. This implies that the tastants within the solutions being licked were more palatable and therefore more licks were able to be performed over the duration of the meal as compared to control subjects who had longer mean pauses between licks and could not consume as much within the given time period. These findings could be due to use of a long-term rig where subjects were given an hour to complete a meal as opposed to a short-term rig where only brief access is given to subjects for consumption of a meal. Conversely, Parker (1991) found that enhancement of saccharin consumption by CDP is not dependent upon the concentrations of the solutions, but instead CDP will non-specifically increase consumption of all solutions. This suggests that the increase of consumption of the solutions (particularly saccharin for this study) is not due to the properties of the solution. Instead it is suggested that CDP interacts with the brain, and thus modifies the taste of the solution making the solution more palatable. More research would need to be conducted in order to distinguish which finding holds more credibility, but both studies suggest that taste of a solution is somehow modified under the effects of CDP.
CDP was the first synthetically created benzodiazepine and therefore, many researchers have studied the effects of CDP. Much research has been produced about the effects of CDP because this drug has been available for the longest amount of time. It is still unclear exactly what brain structures are used in modifying and creating the hyperphagic effects of palatable stimuli seen under the influences of CDP. Researchers have shown how subjects feed under CDP influences, how taste is modified, and other side effects of the drug such as the subject becoming lethargic and slow. Much advancement has been made in benzodiazepines where certain side effects are eliminated. Newer benzodiazepines are more selective in the receptors they bind to and ability to treat what the subject needs to have resolved be it anxiety or otherwise. While much advancement has been made on the reduction of side effects in benzodiazepines, the side effect of hyperphagia exists in many benzodiazepines still today.

Midazolam

Midazolam is another full agonist benzodiazepine developed in the late 1970’s that produces similar hyperphagic effects seen in CDP. Midazolam is classified as an “imidazobenzodiazepine” which is a newer form of benzodiazepine in which the drug is water soluble and has a shorter half life than previous benzodiazepines. Midazolam is a benzodiazepine that is derived from diazepam, but as previously mentioned, unlike diazepam, midazolam is soluble in water and has a shorter half life than diazepam making it more desirable. Midazolam is used in the treatments of acute seizures, insomnia, muscle relaxants and anxiety. Like CDP, midazolam has been studied rigorously and many studies have been produced on the effects of midazolam on animals and humans. Being that midazolam is a full agonist like CDP, all the same brain structures for binding sites are the same. Midazolam is more selective compared to
CDP or diazepam, in that some of the tastants such as salt are selectively enhanced when under the influences of midazolam (Higgs & Cooper, 2005).

While midazolam is more selective than CDP or diazepam, it is still not completely selective. Higgs and Cooper (1998) found that midazolam increases the number of licks and the mean bout of feeding duration due to a manipulation of orosensory and post ingestive factors producing distinctive licking patterns. Dwyer (2009) found similar results to Higgs and Cooper in that animals given midazolam tended to consume all of their solution when under the effects of the drug. Conversely, Cooper and Yearsbury (1986) found that midazolam prolonged the initial period of avid consumption and delayed course of satiety, but did not maintain a hyperphagic effect throughout a 30 minute test period. This finding is a major difference from that of CDP because the hyperphagic effects are much less when taking midazolam, and thus less feeding is likely to occur with fewer drug effects. Fedeli et al. (2009) found that higher doses of the drug cause hyperphagia earlier than when lesser doses are administered, but overall animals consume more solution than animals not treated with the drug. This information is different from that found by Cooper and Yearbury (1986) in that hyperphagia is produced but not maintained, but Fedeli et al., (2009) found that midazolam produces hyperphagic effects similar to older drugs, like CDP, with a smaller dose. Fedeli et al. (2009) does produce an interesting point in that higher doses of midazolam are likely to produce their effects sooner when compared to lower doses. This is an interesting point because most drugs have a period of time in which it takes for effects to be seen. Fedeli et al. (2009) suggests that with a higher dose of midazolam, the effects will be observed more quickly, but when compared with lower doses of midazolam, more time is required for effects to be observed.
Midazolam has also been found to enhance compatibility components of taste and preference (Higgs and Cooper, 1998). Others studies such as Dwyer (2009) believe that midazolam seems to increase consumptions but not the preference for tastants in solutions. However, Dwyer later states that midazolam increases palatability similarly in all conditions, but high concentrations of drugs cause the increases of palatability more quickly. Higgs and Cooper (2005) found similar results to Dwyer in that midazolam enhances palatability in absence of drug influences, like drug-induced hyperphagia, and midazolam altered the recognition and response of aversive stimuli. Both studies suggest that midazolam influences the palatability of substances when ingested thus making the substances more desirable. While research suggests that midazolam influences palatability, Dwyer (2009) also suggests that midazolam does not actually influence the expression of learned tasted preferences, or tastants that the subject has learned to find palatable or aversive. This is an important finding in that palatability of substances is affected, but midazolam will not change preferences of tastes that have already been associated.

Midazolam is very similar to the earliest benzodiazepines in that many benzodiazepines treat the similar symptoms. With midazolam being an older form of benzodiazepine (as compared to present day), many studies have been able to be conducted on it. Midazolam, like CDP, has been found to induce hyperphagia of substances, and increase palatability of ingested substances. As with CDP, research has suggested certain areas of the brain, such as the brain stem and fourth ventricle, may provide a role in the side effects of benzodiazepines such as hyperphagia and becoming slow. As science progresses and better more selective drugs are produced, exact functions of such mechanisms will be explained in time. Since the development of midazolam, newer benzodiazepines have been produced and have eliminated more side effects similarly to the way midazolam reduced side effects from CDP.
Bretazenil

Bretazenil is an “imidazopyrrolobenzodiazepine” partial agonist derived from the benzodiazepine family that was developed in 1988. As mentioned previously, partial agonists such as bretazenil and abecarnil, bind with high affinity to receptors and generally exert both agonistic benzodiazepine properties and antagonistic benzodiazepine effects on GABA-\(\text{A}\) receptors. Different from CDP and midazolam, in addition to hyperphagic effects, bretazenil has anorectic effects (Cooper & Barber, 1993). Partial agonists are a major development in the benzodiazepine family because they retain the anxiolytic and anti-convulsant properties of traditional benzodiazepines but with fewer side effects, such as only affecting food consumption and not water or solution intake (Cooper & Barber, 1993). Weertz, Macey, & Miczek (1999) have found that bretazenil produces anti-convulsant properties at much lower doses than full agonists, and affinity for benzodiazepine receptors is ten times greater in partial agonists than full agonists. This supports the goal of partial agonists to be more effective than full agonists by being more selective and requiring less of the drug to have beneficial effects.

Bretazenil has been found to be more potent in increasing food consumption than CDP (Weertz, Macey, & Miczek, 1998). This finding is odd because bretazenil is supposed to have less intense side effects when comparing side effects to that of CDP. Conversely, Weerts, Macey, & Miczek in the same study also found that bretazenil matches the maximal hyperphagic effects of a full agonist at a lower dose. This finding is supportive of the overall goal of a partial agonist. Due to bretazenil being more selective than older benzodiazepines, the partial agonist is able to be more efficient in treating symptoms with less of the drug needed to achieve the desired effects.
Currently, many researchers believe that benzodiazepines increase the palatability of substances. Challenging this belief, Weertz, Macey, and Miczek (1999) found that benzodiazepines directly stimulate appetite instead of increasing feeding suppressed by aversive consequences when benzodiazepines appear to increase the duration of feeding and the amount of food that is consumed. This finding is different from many other studies where researchers believe that benzodiazepines affect the palatability of desirable foods. This difference may be due to the different drugs or the difference between partial and full agonists. As reported in Cooper and Barber (1993), Bretazenil and other partial inverse agonists, have been found to produce an anti-dipsogenic effect. This suggests that bretazenil may affect food intake but water consumption is not excessive (Cooper & Barber, 1993). This suggestion about partial inverse agonists is different from previous drugs. Previous benzodiazepines have induced hyperphagia and increased water consumption. The partial inverse agonists do not increase water consumption but do still increase food consumption. This ability to eliminate excessive consumption of water is a major difference from previous drugs and as modern medicine has evolved, side effects such as excessive consumption of water have been able to be eliminated.

Bretazenil is a more modern benzodiazepine from previous drugs that have been available. Being one of the first partial agonists, bretazenil is designed to better control for certain factors, and is much more potent that previous benzodiazepines. Multiple studies have found that bretazenil is able to treat symptoms at lower doses of drug than former benzodiazepines. While bretazenil is more efficient in treating symptoms, the side effect of hyperphagia is still present. From current studies, it is unknown exactly how long the hyperphagia lasts or if it is caused by an increased appetite or increased palatability of desirable substances.
foods. More research needs to be conducted in order to determine a more definitive what causes the hyperphagia.

Abecarnil

Abecarnil is a partial agonist derived from the β-carboline family. Different from previously mentioned benzodiazepines, it is not actually a benzodiazepine. Abecarnil is called an anxioselective drug, retains selected benzodiazepine therapeutic reactions but with fewer side effects and the chemical structure of abecarnil when compared to more traditional benzodiazepines is completely different (Cooper & Ridely 2005). β-carboline specifically provides anxiolytic and anti-convulsant properties. Effects of abecarnil are present at the receptor sites and similar to bretazenil, and much lower doses of the drug are necessary to obtain desired effects (Cooper & Greenwood, 1992). Essentially, Cooper and Greenwood are stating that abecarnil is effective as an anxiety reducing or an anti-seizure medication. In these regards, abecarnil is very similar to actual benzodiazepines.

Similar to regular benzodiazepines, abecarnil produces hyperphagic effects. Cooper and Greenwood (1992) found that abecarnil produced some hyperphagic effects such as preferred consumption of saline and saccharin solutions that are selectively enhanced, but there was no effect on water intake. This finding is similar to that of Cooper and Barber (1993) and water consumption concerning bretazenil. The difference between the two drugs is important in that one (bretazenil) is actually a benzodiazepine, but abecarnil is not a benzodiazepine. Also, abecarnil does not have any contradicting studies suggesting that water intake is actually affected when under the influences of the drug. Like midazolam, abecarnil has been found to be effective with specific doses, in that with less medication, desired effects can be observed. However,
abecarnil has more immediate effects that take less time to observe than what had been previously viewed with midazolam (Cooper & Ridley, 2005). This difference is most likely due to the newer developments and selectivity of abecarnil as compared to midazolam which is older and less selective than the newer non-benzodiazepines.

It has been suggested that benzodiazepines act to reduce the local rate of licking, but this effect is pharmacologically dissociable from the hyperphagic or hyperdipsic effects of benzodiazepines, but abecarnil was found to do the same as traditional benzodiazepines in this regard (Cooper & Ridley, 2005). This finding is important in that Cooper and Ridley (2005) suggest that for benzodiazepines as well as abecarnil, rates of licking appear to not be linked pharmacologically to the hyperphagic or hyperdipsic side effects of the drugs. Cooper and Ridley suggest that these side effects are not pharmacologically linked because licking behavior can be viewed immediately after administration of the drug. This is a strange proposition because logically, the more of a substance the subject licks, the more substance the subject can potentially consume leading to hyperphagia or hyperdipsia. Many studies have viewed both hyperphagic and hyperdipsic side effects as one in the same and have not seen the feeding behaviors and intense thirst or hunger as separate side effects. More research would be beneficial in deciphering if feeding responses when under influences of abecarnil are pharmacologically dissociable from the hyperphagic and hyperdipsic side effects produced by abecarnil.

Compared to the drugs that have come prior to abecarnil, abecarnil is a completely different drug than previous benzodiazepines. All of the other drugs in this review are derivates of the traditional benzodiazepine with the goal of ever increasing effectiveness and minimizing the side effects that accompany the drug. Abecarnil is not an exception to the hyperphagic effects that accompany traditional benzodiazepines. However, it is much more selective in that
abecarnil requires a lesser dose to produce desired effects and it does not have a similar chemical structure to the traditional benzodiazepine. Abecarnil has produced a new standard for anti-anxiety drugs that had not previously been matched. The issue of hyperphagia does still exist with abecarnil but other side effects such as dependence found with benzodiazepines does not seem to be present with non-benzodiazepines.

Opioids

Opioids are not benzodiazepines or non-benzodiazepines. Opioids are one of the oldest drugs derived from the opium poppy and used for many reasons, especially as analgesics. Different from benzodiazepines, opioids bind to opioid receptors in the central and peripheral nervous systems as well as the gastrointestinal tract. While opioids bind in different receptors and are used for treatment of different symptoms, benzodiazepines and opioids receptors share one aspect in common, they both produce side effects regarding food intake and consumption (Higgs & Cooper, 1997). Additionally, it has been suggested that the action of benzodiazepines is related to endogenous opioid release, and that opioids are able to counteract the effects of benzodiazepine induced hyperphagia (Higgs & Cooper, 1997). Clearly, both benzodiazepines and opioids are different from each other, but the relationship that the two drugs share is interesting.

According to Söderpalm and Berridge (2000) it has been suggested that benzodiazepines may facilitate feeding by acting on the receptors in the shell of the nucleus accumbens and that the same areas are important for feeding facilitation are also important in benzodiazepine and morphine reception. Later in the same study, it was reported that the nucleus accumbens was found to mediate feeding by opioid and direct GABA agonists but not benzodiazepines. Instead,
benzodiazepines are believed to bind in the 4th ventricle of the brain stem or PBN when regarding feeding habits. Regardless of the brain area that is responsible for the hyperphagic effects, both of the drugs affect ingestive behavior. Söderpalm and Berridge (2000) suggested in their study that morphine increased food intake by 150 percent. Benzodiazepines commonly increase ingestive behaviors, but it has not been reported exactly how much more benzodiazepines.

Both benzodiazepine and opiod receptors agonists have shown to enhance food intake of palatable stimuli. Na, Morris, and Johnson (2012) reported that opioid receptors modify the intake of sodium. In the same study it was reported that morphine, administered by an I-O cannula, decreased negative affective responses to saline and was found to enhance positive hedonic responses similar to those with benzodiazepines. These responses are believed to be due to acting on μ-receptors as well as other receptors simultaneously. Benzodiazepines do not activate μ-receptors because opioids are the activating substance for those receptors. However, the two receptors must somehow be related for in Higgs and Cooper (1997), it was suggested that opioids are able to block the side effects of benzodiazepines when opioids are administered after the benzodiazepine. If what Higgs and Cooper found is accurate, then opioids are acting similarly to what an inverse agonist found in the benzodiazepine family would do.

Higgs and Cooper (1997) state that benzodiazepines are related to endogenous opioid release and the same endogenous opioids play a role in food rewards. This finding explains why hyperphagic effects are present with opioids because the chemicals released from the opioids view and understand food as a desirable reward. If food is viewed as a reward, it would make sense that palatable and desirable foods are consumed more because aversive foods would not produce the same rewarding effect. This finding is partially supportive of what Na, Morris, and
Johnson (2012) found where there was an increased response to sucrose, quinine, umami (Monosodium glutamate) and salty tastes. The only part of this finding that is not supportive with Higgs and Cooper’s statement about a food reward is an increased response to quinine. Typically this bitter response is avoided by subjects and seen as aversive where Na, Morris, and Johnson (2012) state that quinine was found to have an increase in palatability. This finding is different from many other studies. Many other studies such as Higgs and Cooper (1997) suggest that aversive stimuli such as quinine under drug influences. Na, Morris, and Johnson found different results where drugs made quinine palatable. This may be due to the concentration of quinine used. More research would be needed to determine what makes quinine aversive or palatable under drug influences.

At the time there is not believed to be a neural substrate for opiod and benzodiazepine interactions in the determination of palatability (Higgs & Cooper, 1997). It is believed that benzodiazepines and opioids both produce hyperphagic effects of palatable stimuli even though the drugs treat different symptoms. The connection between the drugs has yet to be specifically determined, but according to Higgs & Cooper (1997) endogenous opioid receptors may be involved specifically in the palatability effects seen in benzodiazepine receptor agonists. This insinuates that opioid receptors may play a role in the side effect produced by benzodiazepines of desirable tastant palatability. More research is necessary to determine what the exact role of opioid receptors and benzodiazepines may be. Research would also be interesting to see if a relationship between opioids and non-benzodiazepines such as abecarnil exist.

Conclusion
Throughout the years, modern medicine has made many strides in developing new and more selective benzodiazepines. Chlordiazepoxide (CDP) was the first synthetically created benzodiazepine and has had much research conducted on it due to the length of time it has been around. CDP is not a very selective drug and was a precursor to many of the newer benzodiazepines. CDP provided a foundation for more research and room to develop a newer and better drug. Research of CDP provided the initial observations of the hyperphagic effects found in many of the benzodiazepines. From CDP, midazolam was produced. Midazolam was produced to have fewer side effects than CDP, and to an extent, succeeded. Some of the more severe side effects associated with CDP such as nausea was eliminated, but hyperphagia still persisted. From midazolam came bretazenil in the late 1980’s.

Bretazenil was a major improvement from earlier drugs like CDP and midazolam. Bretazenil was one of the first partial agonists and therefore it provided anti-anxiety medications that were less addictive, it could deliver the intended effects of the drug with a smaller dose, and both of these advancements were possible because bretazenil was more selective to receptors in the brain when compared to previous drugs. Abecarnil is a non-benzodiazepine in that it works similarly to a benzodiazepine and treats the same symptoms, but it has a completely different chemical structure than “actual” benzodiazepines. Abecarnil is more selective than bretazenil or other benzodiazepines, and requires an even lesser dose to obtain the desired effects of the drug. Non-benzodiazepines are believed to completely eliminate dependence seen in other drugs. Abecarnil and other non-benzodiazepines have set a new standard of anti-anxiety drug not previously matched by actual benzodiazepines.

Opioids are not technically benzodiazepines, and treat different symptoms, but they do produce similar hyperphagic effects of palatable tastants. This is believed to be because opioids
are believed to bind similarly to that of benzodiazepines and non-benzodiazepines, even though opioids bind to mu and kappa receptors while benzodiazepines bind to GABA-\(A\) receptors. The exact connection between opioids and benzodiazepines has yet to be determined, but some researchers such as Higgs and Cooper (1997) believe endogenous opioid receptors may be involved in palatability effects seen in benzodiazepine receptor agonists.

With new developments of drugs occurring often, the ability to produce a very selective benzodiazepine with no side effects may be possible one day. Currently, work would still need to be done to produce a drug with no side effects. Also, a better understanding of receptor binding and effects would be necessary to create such a drug. Using benzodiazepines in comparison with opioids has proven to show some relationships with binding structures and effects. It would be interesting to compare opioids with the non-benzodiazepine drugs that have different chemical structures, such as abecarnil, and see if the same effects persist as with regular benzodiazepines. With more time and research, such discoveries will be made. These discoveries can produce new drugs and give a better insight to the ones currently in use.
References


