Behavioral Pharmacology of Sedatives, Hypnotics, and Anxiolytics

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The purpose of this chapter is to review the behavioral pharmacology and abuse liability of commonly prescribed anxiolytics and hypnotics. More specifically, this chapter reviews the behavioral pharmacology and abuse liability of commonly prescribed benzodiazepines (e.g., alprazolam, diazepam, estazolam, lorazepam, temazepam, and triazolam) and nonbenzodiazepine anxiolytics-hypnotics (e.g., buspirone and zolpidem). The behavioral pharmacology and abuse liability of the benzodiazepines is not exhaustively reviewed since such a review is beyond the scope of this chapter, and comprehensive reviews have previously been published (Woods, Katz, & Winger, 1987, 1992). Instead, this chapter focuses on studies that attempted to determine putative differences between benzodiazepines. This chapter then reviews the behavioral pharmacology and abuse liability of two nonbenzodiazepine compounds marketed for the treatment of anxiety and sleep disorders: buspirone and zolpidem, respectively. Buspirone was the first pyrimidinylpiperazine derivative marketed for the treatment of anxiety disorders, while zolpidem was the first imidazopyridine derivative marketed for the treatment of sleep disorders. Only studies that directly compared these drugs with a benzodiazepine are reviewed in an attempt to determine if these nonbenzodiazepine compounds have an improved abuse liability profile. Both nonhuman and human studies are reviewed.

Defining and Characterizing Abuse Liability

Many drugs, including commonly prescribed anxiolytics and hypnotics have liability for abuse. That is, commonly prescribed anxiolytics and hypnotics are often taken for nonmedical purposes at supratherapeutic doses. Commonly prescribed anxiolytics and hypnotics also have liability of abuse. That is, they produce adverse effects such as physiological dependence and performance impairment. The...
relative abuse liability of a drug is an interactive function of its liability for and of abuse (Brady & Ator, 1990; R. R. Griffiths, Lamb, Ator, Roache, & Brady, 1985).

Preclinical studies with nonhuman laboratory animals typically assess a drug’s liability for abuse by determining whether it maintains self-administration (Brady & Ator, 1990; R. R. Griffiths et al., 1985). In a typical self-administration experiment, nonhuman laboratory animals receive oral or intravenous administrations of drug or vehicle (i.e., placebo) contingent on emitting a response (e.g., lever press). Drugs that maintain rates of self-administration greater than those observed with vehicle are deemed to be reinforcers. Importantly, there is a high degree of concordance between drugs that maintain self-administration and function as reinforcers in nonhuman laboratory animals and those that are abused by humans (Fischman & Mello, 1989). Preclinical laboratory studies also characterize a drug’s interoceptive or discriminative stimulus effects using drug-discrimination procedures (Glennon, Jarbe, & Frankenheim, 1991). In a typical drug-discrimination experiment, a subject learns one response (e.g., press right lever) following the injection of drug and a different response (e.g., press left lever) following the injection of vehicle. Following training, novel drugs can be substituted for the training drug to determine whether they share discriminative stimulus effects. A drug is inferred to have at least some liability for abuse if it substitutes for a drug known to be abused (Preston & Bigelow, 1991). Finally, preclinical studies determine a drug’s ability to produce physiological dependence by chronically treating animals and then abruptly terminating drug administration and observing the animal for symptoms of withdrawal, or by administering an appropriate antagonist to determine whether it precipitates withdrawal.

Self-administration and drug-discrimination procedures adapted for use with human subjects are being used more frequently to determine the liability for abuse of commonly prescribed anxiolytics and hypnotics (R. R. Griffiths, Bigelow, & Liebson, 1979; Kamien, Bickel, Hughes, Higgins, & Smith, 1993). Human laboratory studies also often assess liability for abuse using subject ratings of drug liking, euphoria, and mood (de Wit & Griffiths, 1991; Roache & Griffiths, 1989a). Drugs of abuse typically increase subject ratings of drug liking and euphoria, or produce positive-mood changes. Clinical studies most typically determine a drug’s ability to produce physiological dependence by chronically treating patients, discontinuing treatment, and then observing the patient for symptoms of withdrawal. Human laboratory experiments further determine a drug’s liability of abuse (i.e., adverse effects) using tasks that measure various aspects of human performance (e.g., recall).

Benzodiazepine Compounds

Benzodiazepines are indicated in the treatment of anxiety, sleep problems, and musculoskeletal disorders, and are among the most widely prescribed psychoactive drugs (Hollister, Muller-Oerlinghausen, Rickels, & Shader, 1993). While their abuse liability is low compared to other abused drugs (Katz, Winger, & Woods, 1990; Rifkin, Doddi, Karajgi, Hasan, & Alvarez, 1989; Woods et al., 1987, 1992), there is sufficient evidence documenting that benzodiazepines have some liability for abuse (i.e., they maintain self-administration) and significant liability of abuse (i.e., adverse effects). The nonmedical use of benzodiazepines at supratherapeutic doses is common among individuals with histories of ethanol, opioid, and sedative dependence (Bigelow et al., 1980; Darke, Ross, & Hall, 1995; DuPont, 1988; R. R. Griffiths & Wolf, 1990; Iguchi, Handelman, Bickel, & Griffiths, 1993; Miller & Gianinni, 1991; Navaratnam & Foong, 1990a, 1990b; Sellers et al., 1993; Stitzer, Griffiths, McLellan, Grabowski, & Hawthorne, 1981). Benzodiazepines produce a myriad of adverse effects including physiological dependence and performance impairment (Bowen & Larson, 1993; Curran, 1991; Rush, Higgins, Bickel, & Hughes, 1993a).

Some evidence suggests that the available benzodiazepines may be distinguishable in terms of their abuse liability. First, individuals