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References

Depression and anxiety disorders CHAPTER 3 Benzodiazepines and disinhibition Unexpected increases in aggressive or impulsive behaviour secondary to drug treatment are usually called disinhibitory or paradoxical reactions. These reactions may include acute excitement, hyperactivity, increased anxiety, vivid dreams, sexual disinhibition, aggression, hostility and rage. Examples of causative agents include amfetamines, methylphenidate, benzodiazepines and alcohol. Paradoxical reactions are an important consideration with benzodiazepines because these drugs are used to sedate and tranquillise – a paradoxical reaction is thus the polar opposite of the desired effect. These reactions are also a major problem in general medicine, where drugs such as midazolam are widely used for conscious sedation. In intensive care medicine, benzodiazepine--related disinhibition can be difficult to distinguish from hyperactive delirium.1 How common are disinhibitory reactions with benzodiazepines? The incidence of disinhibitory reactions varies widely depending on the population studied (see ‘Who is at risk?’ below). For example, a meta-analysis of benzodiazepine RCTs that included many hundreds of patients with a wide range of diagnoses reported an incidence of less than 1% (the same as placebo).2 Similarly, an analysis of behavioural disinhibition frequency in a psychiatric unit found no difference between those treated with benzodiazepines and those not.3 However, a Norwegian study that reported on 415 cases of ‘driving under the influence’, in which flunitrazepam was the sole substance implicated, found that 6% of adverse effects could be described as disinhibitory reactions.4 An RCT that recruited patients with panic disorder reported an incidence of disinhibition of 13%.5 Authors of case series (often describing use in high-risk patients) reported rates of 10–20%,2 and an RCT that included patients with borderline personality disorder reported a rate of 58%.6 Most recently, a study of the use of parenteral midazolam for bronchoscopy found that almost 20% of patients exhibited moderate or severe disinhibition.7 Disinhibition is rather problematic to define, so incident rates are correspondingly difficult to determine. Aggression may be considered to be a disinhibition reaction but not defined as disinhibition per se. Aggression is robustly linked to benzodiazepine use both in the long term and after exposure to a single dose.8,9 Other GABA agonists, particularly zolpidem, have also been linked to disinhibition associated with somnambulism, automatism, amnesia and mania.10–13 Who is at risk? Those at risk include people who have learning disabilities, neurological disorders or CNS degenerative diseases,14 those who are young (children or adolescents) or elderly,14–17 have a history of aggression or poor impulse control,6,18 or are at increased risk of experiencing a disinhibitory reaction. The risk is further increased if the benzodiazepine is a high-potency drug (i.e. is active in doses below 1–2mg), has a short half- life, is given in a high dose or is administered intravenously.14,19–21 Some people may be genetically predisposed to disinhibition reactions.22 Combinations of risk factors are clearly important. Low-risk long-acting benzodiazepines may cause disinhibition in high-risk populations such as

children;17 higher-risk,

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