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Clinical Pharmacology of Non-Benzodiazepine Anxiolytics

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LADER, M. *Clinical pharmacology of non-benzodiazepine anxiolytics.* PHARMACOL BIOCHEM BEHAV 29(4) 797–798, 1988.—Non-benzodiazepine anxiolytics can be conveniently divided into those which are not primarily used as anxiolytics, those which pharmacologically but not chemically resemble benzodiazepines, and those which are novel both chemically and pharmacologically. The former include antidepressants, antipsychotic drugs, antihistamines and beta-adrenergic antagonists. The second group comprises a variety of compounds which act on the benzodiazepine/GABA complex and include alpidem and zuriclone. The most important of the non-benzodiazepine anxiolytics is buspirone, which seems to act on 5-HT mechanisms. The field of anxiolytic therapy is changing rapidly. New drugs are being introduced and the use of old ones questioned. It is hoped that drugs will be developed which are not only effective and safe with no sedation, but also with little or no propensity to dependence and abuse.

Non-benzodiazepine anxiolytics Buspirone Alpidem Benzodiazepines

THE drug treatment of anxiety as a symptom and as a syndrome largely involves the use of a benzodiazepine. These compounds supplanted the substituted diol substance meprobamate which enjoyed a brief vogue in the 1950s. Also rendered obsolescent were the barbiturates which had been introduced at the beginning of the century and which had been the mainstays of treatment for many years. A point whose relevance will become apparent later is that all these compounds are related pharmacologically; in particular, cross-tolerance is found between the benzodiazepines, the barbiturates, meprobamate and older drugs such as paraldehyde, chloral derivatives and ethanol.

Non-benzodiazepine anxiolytics can be conveniently divided into those which are not primarily used as anxiolytics, those which pharmacologically but not chemically resemble benzodiazepines, and those which are novel both chemically and pharmacologically. Each class will be outlined in turn, with most emphasis on the last.

NON-PRIMARY ANXIOLYTICS

A wide range of drugs have been used to assuage anxiety and include:

Antidepressants. Many antidepressants are sedative mainly because of their pronounced antihistaminic effects, although other properties such as adrenergic blockade and effects on serotonin uptake may be operative. Efficacy is quite substantial.

Antipsychotic drugs in low dosage have been used [4] extensively to treat anxiety. However, both autonomic and extrapyramidal side effects limit their usefulness.

Antihistamines are popular sedatives for anxiety in children but are too sedative for general use in adults.

Beta-adrenergic antagonists have been used for almost 20 years to lessen symptoms of anxiety. The most responsive symptoms are those mediated by the beta-adrenergic sympathetic system, namely, palpitations, gastro-intestinal upset and tremor. In addition, such symptoms must be pivotal to the anxiety syndrome for amelioration of such symptoms to lead to an adequate clinical response [6].

Miscellaneous. Other drugs used as anxiolytics have included scopolamine, chloral, paraldehyde and lithium [3].

BENZODIAZEPINE-LIKE ANXIOLYTICS

As stressed earlier, the benzodiazepines have many pharmacological properties in common with their predecessors, the barbiturates and ethanol, the main improvement being safety in overdosage. In biochemical terms, the actions are also similar with influences on or about the macromolecular complex of benzodiazepine/GABA receptor and chloride ionophore [7]. A large number of newer compounds have been developed with a view to having anxiolytic efficacy with little or no sedative actions. Most, however, act on the benzodiazepine/GABA complex and are therefore basically benzodiazepine-like. They include tracazolate and its congeners, zuriclone, pipequaline, and alpidem. The last will be described as an example of this type of compound.

Alpidem has putative anxiolytic properties in doses of 50–75 mg twice a day. Its clinical pharmacology resembles that of the benzodiazepines but definite differences exist. In our own work [1], we noted an EEG profile typical of a benzodiazepine. Overall psychomotor and cognitive performance was much less impaired by alpidem than by a therapeutically equipotent dose of lorazepam. In particular, memory was little affected by alpidem.

Thus, alpidem should prove to be an effective anxiolytic with minimal sedative effects at anxiolytic doses. However, it is likely to induce the same long-term adverse effect, dependence with withdrawal problems, as the benzodiazepines.

NON-BENZODIAZEPINE-LIKE ANXIOLYTICS

A few compounds are being developed which are not only chemically different (in itself not important) but which lessen anxiety by mechanisms that do not directly involve GABA effects. The most advanced compound is buspirone which was introduced in West Germany in 1985 and in the USA in late 1986. It was originally synthesised in the search for a better antipsychotic drug but its antidopamine properties are probably not instrumental in its antianxiety profile. Instead, its mode of action appears to reflect its agonism of 5-HT_{1A} receptors, thereby increasing inhibitory serotoninergic influences.

In studies in normal subjects, buspirone is only sedative in supratherapeutic doses and it hardly impairs psychomotor, cognitive or memory functions [2], nor does it interact significantly with ethanol. Clinically it is equipotent with diazepam and about equals it in efficacy as an anxiolytic although buspirone lacks muscle relaxant and anticonvulsant actions.

The possibility of abuse and dependence on buspirone has received especial attention. Such animal models as there are suggest that it should not induce an abuse problem like, for instance, the barbiturates. Also, no cross-tolerance to the barbiturates or to the benzodiazepines could be demonstrated. In clinical studies involving the double-blind substitution of placebo, long-term (6 months) use of buspirone was not followed by withdrawal problems as was that of clorazepate. Thus, intermittent use with short courses of treatment should be feasible. However, the lack of cross-tolerance with the benzodiazepines means that long-term benzodiazepine users cannot be easily switched to buspirone as withdrawal symptoms will not be suppressed. Indeed, clinical data show that buspirone appears definitely less efficacious in patients with prior experience of benzodiazepines than in those starting anxiolytics for the first time [5].

Another putative anxiolytic is ritanserin, which is a 5-HT_2 antagonist, thereby lessening the excitatory influences of these serotonin pathways. Again, it should prove non-cross-tolerant to the benzodiazepines with the attendant problems of usage encountered by buspirone.

CONCLUSIONS

This brief review shows that the field of anxiolytic therapy is undergoing rapid change. The indications for older compounds are being refined; newer more "anxioselective" compounds are being developed with different profiles of action; and totally novel drugs are entering the physician's armamentarium. Simultaneously, the widespread use of all anxiolytics is being questioned. The indications for drug treatment will be clarified over the next decade: those patients who need pharmacological intervention will be treated with drugs which are not only effective and safe with no sedation, but also with little or no propensity to dependence and abuse.

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