Serotonin 5-HT\textsubscript{1A} Agonists
A Comparative Review

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Summary

In 1980, buspirone was found to have anxiolytic potential. This finding initiated the development of the azapirones – highly serotonin 5-HT\textsubscript{1A} agonists. The balance of evidence suggests that the azapirones act as partial agonists postsynaptically, but as full agonists presynaptically in the dorsal raphé. This review focuses mainly on agents for which there are published clinical trial data.

Numerous studies have shown that buspirone, gepirone and ipsapirone are as effective as the benzodiazepines in the treatment of generalised anxiety. However, they have a slower onset of action. The azapirones have a completely different adverse reaction profile (dizziness and gastric complaints) compared with the benzodiazepines (sedation, memory loss and withdrawal dependency).

Several controlled studies have shown that the azapirones are effective in depression, particularly of the melancholic type. They have an adverse effects profile similar to, but less severe than, the selective serotonin reuptake inhibitors and different to that of the tricyclic antidepressants.

Buspirone has not yet proven to be effective in panic disorder. However, gepirone, ipsapirone and other azapirones may be more effective in this disorder. Early studies indicate promising results for buspirone in the treatment of obsessive-compulsive disorder. Clinical trials in alcoholism are equivocal. Further studies of this class of drugs in the treatment of social phobia, post-traumatic stress dis-
order, premenstrual syndrome, and compulsive and aggressive disorders are in progress.

A principle drawback with this class of drug is their short half-life. However, sustained release preparations are being developed.

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1. Serotonin in Psychiatry

Abnormalities in serotonin (5-hydroxytryptamine; 5-HT) neurotransmission appear to be involved in several psychiatric conditions, including affective, obsessive-compulsive, panic and seasonal affective disorders.[1] Since the initial hypothesis that serotonin might be related to mental diseases was postulated by Wooley and Shaw in 1954,[2] major milestones in the serotonin story have emerged. One of these was the discovery of multiple serotonin receptors by Peroutka and Snyder in 1979.[3] A recent overview of serotonin receptor function notes that 5-HT1A,B,D, 5-HT2A,B, 5-HT3 and, probably, 5-HT4 receptors exist.[4]

Buspirone (fig. 1) was synthesised in 1972 by Wu and Rayburn,[5] and was found to be a 5-HT1A agonist. However, the agent failed as an antipsychotic and development was halted until it was administered to aggressive Rhesus monkeys and a calming effect was observed.[6] It was subsequently reintroduced as an anxiolytic, and heralded a new class of psychotropic agents, the azapirones. Since that time, numerous publications have examined the pharmacological, neurochemical and clinical profiles of this molecule.

At present, buspirone is the only one of this class of agents that has been internationally marketed. Gepirone and ipsapirone (fig. 1) are being extensively tested in Europe and North America, and tandospirone is still in the process of development. As well as these agents, which are all azapirones, several other 5-HT1A agonists are being developed. These include flesinoxan, an agent currently under study for depression, binospirone (MDL-73005-EF), NAN-190, BMY-7378 and spiroxatrine.

2. Neurochemistry of 5-HT1A Receptors and the Azapirones

The 5-HT1A receptor subtype was first identified as a binding site for [3H]serotonin, and the antipsychotic spiperone was also found to have a high affinity for this site.[7] The first specific ligand, a potent agonist, was 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT).[8,9] The azapirones are a new class of molecule with particular affinity for the 5-HT1A receptor.[10-13]

![Fig. 1. Structural formulae of buspirone, gepirone and ipsapirone, and their common metabolite 1-(2-pyrimidinyl)piperazine (1-PP).]