Gepirone in Depression and Anxiety Disorders
An Initial Appraisal of its Clinical Potential

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Summary

Gepirone is an azapirone derivative with partial agonist activity at the post-synaptic serotonin (5-hydroxytryptamine) 5-HT1A receptor. In contrast to buspirone, gepirone lacks appreciable \textit{in vitro} affinity for the dopamine D2 receptor, and exhibits only limited dopaminergic activity \textit{in vivo}. The drug is active in several animal models considered predictive of antidepressant and anxiolytic activity, and is currently under development as a potential treatment for affective and anxiety disorders. The limited number of controlled clinical trials performed to date indicate that gepirone is of superior therapeutic efficacy to placebo on short term (≤10 weeks) administration to outpatients with generalised anxiety disorder (dosage range ≤60 mg/day) and major depressive disorder or atypical depression (dosage range ≤90 mg/day). The antidepressant effect of gepirone appears to be additional to its anxiolytic effect. As with buspirone, onset of the anxiolytic effect of gepirone appears to be delayed (≈2 to 4 weeks) relative to that of the benzodiazepines. The tolerability profile of gepirone mirrors that of
Buspirone: gepirone is nonnonsedating, lacks anticholinergic effects, and appears to be of low abuse potential. Gepirone has a possible role in the treatment of major depression, particularly that of the milder, non-endogenous or non-melancholic subtype, major depression associated with generalised anxiety, atypical depression, and chronic generalised anxiety disorder.

Gepirone, a structural pyrimidinyl piperidine-dione analogue of the nonbenzodiazepine anxiolytic buspirone (fig. 1), is a selective serotonin (5-hydroxytryptamine) 5-HT1A receptor agonist with anxiolytic and antidepressant properties. The drug was first synthesised in 1979 and patented for use as an anxiolytic in 1983 and as an antidepressant in 1988; it is currently in Phase III of clinical development.

1. Overview of Pharmacological Properties

1.1 Pharmacodynamic Properties

In vitro, gepirone inhibits specific binding of the radioligand [3H]8-hydroxy-di-N-propylamino-tetralin ([3H]8-OH-DPAT) to the 5-HT1A receptor in rat brain preparations [concentration required for 50% inhibition (IC50) = 115 to 260 nmol/L], showing approximately 5-fold lower potency than buspirone. In contrast to buspirone, gepirone has negligible in vitro affinity for the dopamine D2 receptor.

In vivo, gepirone labels those limbic (septo-hippocampal) structures associated with high 5-HT1A receptor densities, acting as a full agonist at the presynaptic (somatodendritic) 5-HT1A autoreceptor and a partial agonist at the postsynaptic 5-HT1A receptor.

On long term administration in the rat, gepirone differentially desensitises the presynaptic 5-HT1A autoreceptor, thereby reducing serotonergic autoregulatory inhibition and enhancing tonic activation of postsynaptic 5-HT1A receptors.

Gepirone additionally down-regulates the postsynaptic 5-HT2 receptor in the frontal cortex, a property common to many antidepressants but does not affect the β-adrenoceptor.

In common with other azapirones, gepirone reduces neuronal activity in the dorsal raphe nucleus and serotonin release in the hippocampus of the rat. Gepirone additionally increases firing of noradrenergic neurons in the locus ceruleus and shows α1-adrenergic agonist activity on vascular smooth muscle. In contrast, the metabolite, 1-(2-pyrimidinyl)-piperazine (1-PP), binds selectively to α2-adrenoceptors in vitro and has significant α2-adrenergic antagonist activity in vivo. Gepirone increases striatal dopamine turnover and exhibits dopamine D2 agonist activity in the pituitary, effects presumably related to the removal of the inhibitory influence of serotonergic systems on nigrostriatal dopamine activity. Single dose administration of gepirone in the rat produces the '5-HT behavioural syndrome' associated with 5-HT1A receptor stimulation, and reduces the behavioural response (head-shaking/head-twitch) to 5-HT2 receptor stimulation. Gepirone also increases feeding behaviour in the nondeprived rat, an effect attributable to inhibition of serotonin release.

Fig. 1. Structural formulae of gepirone and buspirone.