Serotonergic drugs in animal models of anxiety: An update

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Serotonin
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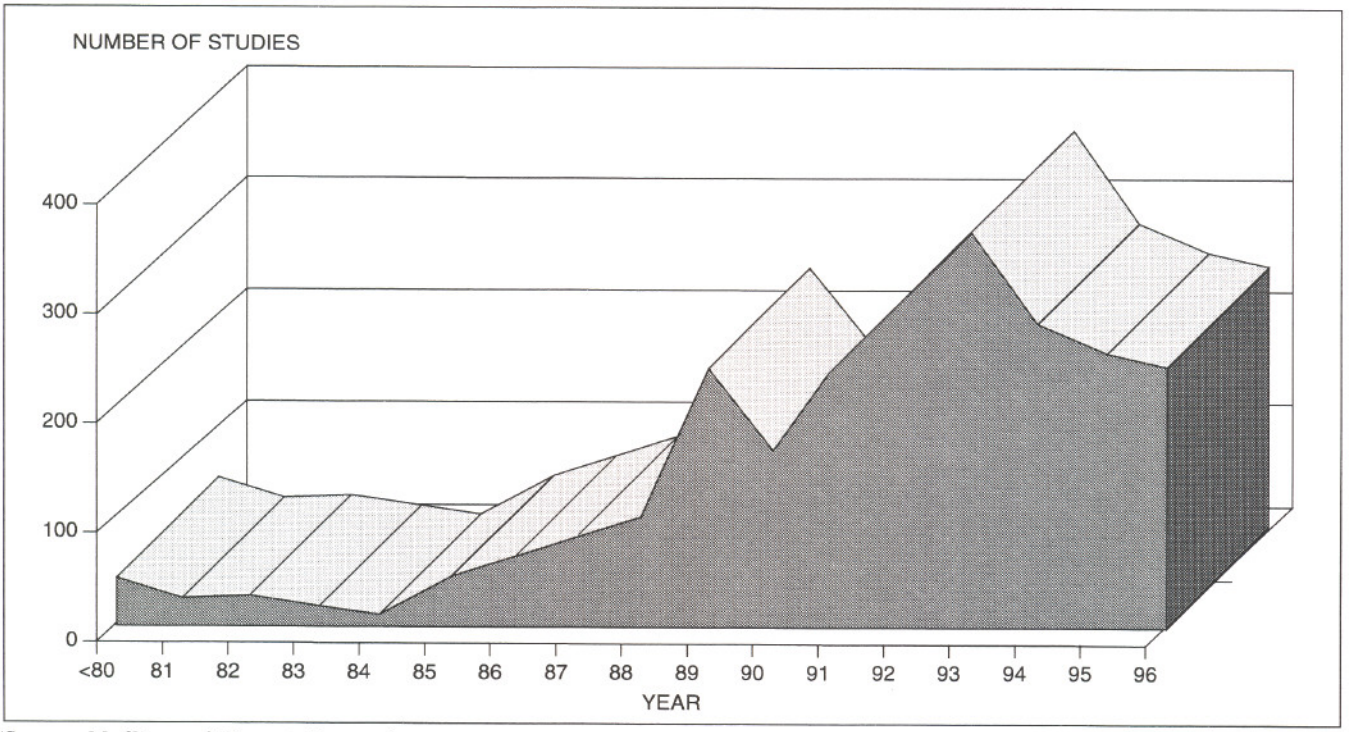
The preclinical literature relating to 5-HT and anxiety is vast. Nearly 2500 experiments have been performed during the last two decades. Much attention has focused on the behavioral effects of selective 5-HT_{1A} receptor ligands, but interest in drugs combining 5-HT_{1A} agonistic, 5-HT_2 antagonistic and/or 5-HT re-uptake inhibitory properties is increasing. Data on the efficacy of selective 5-HT_2 and 5-HT_3 receptors antagonists in anxiety models have not been convincing and seem to indicate that these drugs may be of limited therapeutic utility in the clinical management of anxiety disorders.

Introduction

5-Hydroxytryptamine (5-HT) is a neurotransmitter involved in the regulation of a variety of physiological functions including aggression, appetite, mood, pain, sexual function and sleep. Pathological states such as impulsive violence, migraine, depression and anxiety are often associated with central 5-HT dysfunction [1]. 5-HT binds at multiple sites. At the present time, the 5-HT receptor family can be split into seven groups: 5-HT_1-like, 5-HT_2-like, 5-HT_3, 5-HT_4, 5-ht_5, 5-ht_6 and 5-HT_7. Within the 5-HT_1 family, five subtypes have been described, namely 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F}. The 5-HT_2 group divided into three sub-types, namely 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} [2]. Of these, at least the 5-HT_{1A}, 5-$HT_{2/2C}$ and 5-HT_3 receptors have been implicated in anxiety. In addition, the inhibition of 5-HT re-uptake can achieve anxiolytic activity [3]. Although benzodiazepines remain the mainstay of treatments for anxiety disorders, the last decade has seen preclinical research in this area focused mainly upon compounds modulating 5-HT neurotransmission. Nearly 2500 experiments have been carried out since the initial study of Aprison and Ferster in 1961. These revealed potential anxiogenic-like effects of the 5-HT precursor 5-hydroxytryptophan in a pigeon conflict procedure [4]. Figure 1 shows that the number of experiments involving 5-HT-related drugs in animal models of anxiety has increased during the period 1985 to 1993. However, since then the number of studies has declined steadily. In 1996, approximately 250 papers dealing with 5-HT and anxiety were published, compared to 1993 when the number exceeded 350. Figure 2 reveals that nearly 50% of the experiments with 5-HT compounds involved 5-HT_{1A} receptor ligands, while investigations involving 5-HT_2 agents, 5-HT_3 agents, and 5-HT re-uptake inhibitors (SRIs) amounted to 15%, 13% and 7%, respectively of the total number of studies relating to 5-HT and anxiety in animals. A more detailed analysis (Figure 3) indicates that the 5-HT_{1A} receptor partial agonist buspirone (Bristol-Myers Squibb) was the most considered drug. Among the 5-HT_2 compounds, experiments have

Figure 1: 5-HT and anxiety studies in the primary literature, 1961 to 1996



(Source: *Medline and Current Contents*)

have mainly focused on the behavioral effects of the non-selective 5-$HT_{2/2B/2C}$ receptor antagonist ritanserin (Janssen Cilag), whereas the selective 5-HT_3 receptor antagonist ondansetron (Glaxo Wellcome) has been the most extensively studied 5-HT_3 agent to date. Finally, with regard to the SRIs, the majority of these procedures has involved the mixed 5-HT/norepinephrine re-uptake inhibitor imipramine.

The present article provides an update of the developments in preclinical research involving 5-HT-modulating agents and anxiety. The emphasis will be on a review of the effects of recently released 5-HT compounds including selective 5-HT_{1A} ligands, selective 5-HT_2 and 5-HT_3 antagonists, mixed 5-HT_{1A} /5-HT_2 ligands and SRIs (Table 1).

Behavioral effects of selective 5-HT_{1A} receptor ligands

The 5-HT_{1A} receptors are located both presynaptically on the 5-HT cell bodies in the raphé nuclei and postsynaptically in several limbic structures including the hippocampus and the amygdala [5]. Activation of presynaptic 5-HT_{1A} receptors results in an inhibition of cell firing and, consequently, a decrease in 5-HT neurotransmission, whereas the activation of postsynaptic 5-HT_{1A} receptors leads to a neuronal inhibition in some limbic structures [6,7]. Both of these actions are claimed to underlie the anxiolytic effects of 5-HT_{1A} receptor ligands [8].

Figure 2: Detailed analysis of the most extensively studied 5-HT drug classes in anxiety models from 1961 to 1996

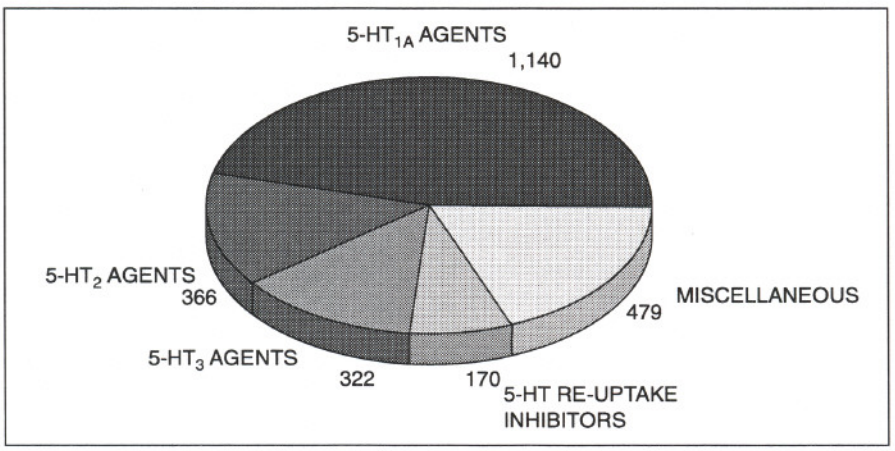


Figure 3: Studies of 5-HT drug classes in anxiety models (1961 to 1996)

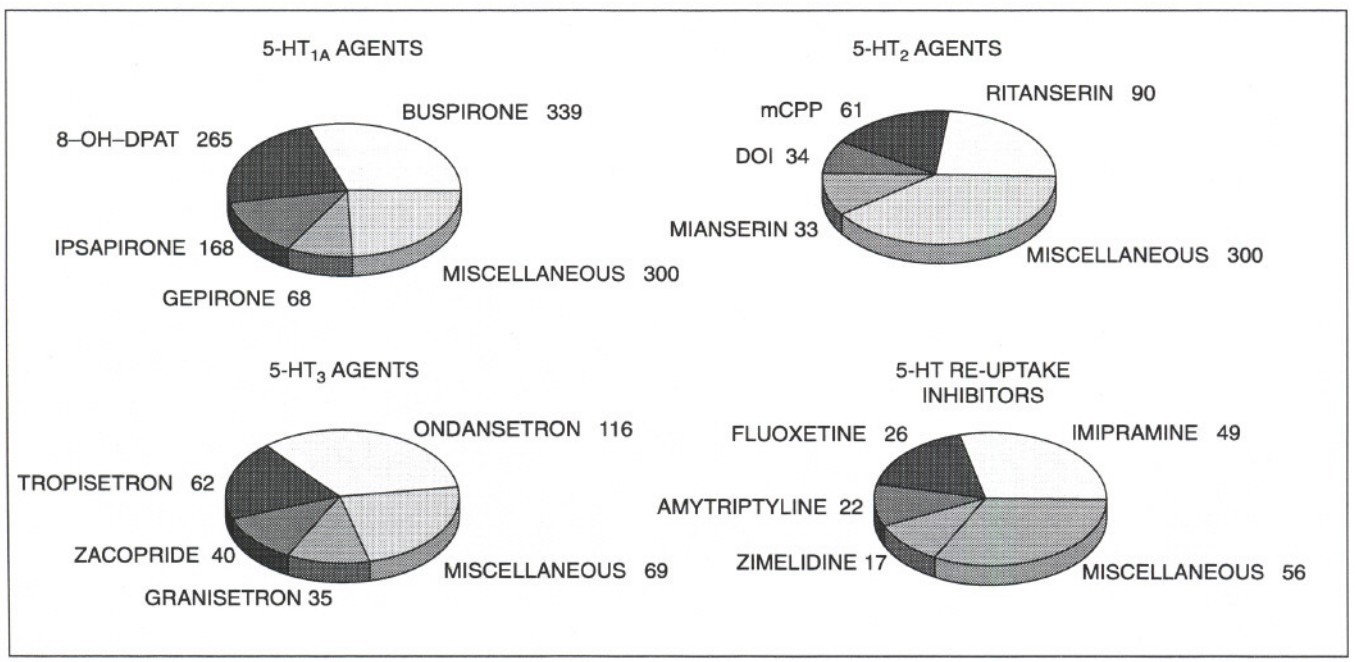


Table 1: 5-HT-interacting drugs currently in development as anxiolytic agents

DRUGS	ACTION	CURRENT PHASE	COMPANY
Alnespirone	5-HT_{1A} agonist	Phase II	Servier
Binospirone	5-HT_{1A} agonist	Phase I	Hoechst Marion Roussel
CP-93393	5-HT_{1A} agonist	Phase II	Pfizer
F-12439*	5-HT_{1A} agonist	Preclinical	Pierre Fabre
Flesinoxan	5-HT_{1A} agonist	Phase III	Solvay Duphar
Gepirone	5-HT_{1A} agonist	Phase III	Mead Johnson
Lesopitron	5-HT_{1A} agonist	Phase II	Esteve
MKC-242	5-HT_{1A} agonist	Phase II	Mitsubishi
NAD-299*	5-HT_{1A} antagonist	Preclinical	Astra
S-14671	5-HT_{1A} agonist	Preclinical	Servier
S-15535	5-HT_{1A} antagonist	Research Tool	Servier
SDZ-216-525	5-HT_{1A} antagonist	Preclinical	Sandoz
Tandospirone	5-HT_{1A} agonist	Launched	Sumitomo
U-93385	5-HT_{1A} agonist	Phase I	Pharmacia & Upjohn
WAY-100135	5-HT_{1A} antagonist	Preclinical	Wyeth Ayerst
Amesergide*	5-$HT_{2/2C}$ antagonist	Phase II	Eli Lilly
BW-723C86	5-HT_{2B} agonist	Preclinical	SmithKline Beecham
CR-1909*	5-HT_{2} antagonist	Preclinical	Rotta
Deramciclane	5-$HT_{2/2C}$ antagonist	Phase I	EGIS
Ritanserin	5-$HT_{2/2C}$ antagonist	Phase III	Janssen Cilag
SB-200646A	5-HT_{2C} antagonist	Research Tool	SmithKline Beecham
SB-206553	5-$HT_{2B/2C}$ antagonist	Research Tool	SmithKline Beecham
SB-221284*	5-$HT_{2B/2C}$ antagonist	Preclinical	SmithKline Beecham
SR-46349*	5-HT_{2A} antagonist	Phase II	Sanofi
Ziprasidone*	5-$HT_{2A/2C}$ antagonist	Phase III	Pfizer
Alosetron	5-HT_{3} antagonist	Phase II	Glaxo Wellcome
Itasetron	5-HT_{3} antagonist	Phase III	Boehringer Ingelheim
Mirisetron*	5-HT_{3} antagonist	Preclinical	American Home Products
RS-42358	5-HT_{3} antagonist	Phase II	Roche Bioscience
VA-21B7	5-HT_{3} antagonist	Preclinical	Vita
WAY-100289	5-HT_{3} antagonist	Phase I / discontinued?	Wyeth Ayerst
WAY-100579	5-HT_{3} antagonist	Phase I	Wyeth Ayerst
Zatosetron*	5-HT_{3} antagonist	Phase III	Eli Lilly
Cericlamine*	5-HT re-uptake inhibitor	Phase III	Jouveinal
Duloxetine*	5-HT re-uptake inhibitor	Phase III	Lilly
Adatanserin	5-HT_{1A} agonist/$_{2C}$ antagonist	Phase II	American Home Products
EMD-68843	5-HT_{1A} agonist/5-HT re-uptake inhibitor	Phase I	Merck KGaA
FG-5865*	5-HT_{1A} agonist/5-HT_{2A} antagonist	Preclinical	Pharmacia & Upjohn
FG-5893	5-HT_{1A} agonist/5-HT_{2A} antagonist	Preclinical	Pharmacia & Upjohn
HT-90B	5-HT_{1A} agonist/5-HT_{2A} antagonist	Preclinical	Chugai
S-21357-1	5-$HT_{1A/2A}$ antagonist	Preclinical	Servier

Source: Investigational Drugs *database*, Current Drugs
* Indicates that data on the therapeutic potential of the drug have not yet been published

Buspirone is marketed in Europe and in the USA for the indication of anxiety [9]. It is the first of a class of compounds known as azaspirones. Three analogs of buspirone, namely ipsapirone (Bayer), gepirone (Bristol-Myers Squibb) and tandospirone (Sumitomo) have been successfully used against generalized anxiety disorders (GAD) [10-12] and tandospirone has been recently launched in Japan. Bayer recently discontinued development of ipsapirone for undisclosed reasons. In agreement with these clinical findings, studies in animals have shown that the three compounds displayed an anxiolytic-like action in several animal models of anxiety [3]. Ipsapirone and gepirone reduced anxiety-related responses in animals in more than 80% of cases, and tandospirone displayed a similar action in all 19 experimental investigations. Flesinoxan (Duphar) is another compound with 5-HT_{1A} agonistic activity, reported to be in phase III clinical trials for anxiety. Although published studies in animals systematically reported anxiolytic-like effects of the drug, its efficacy in clinical trials has not yet been clearly established [13].

Several newer compounds with 5-HT_{1A} agonistic activity are reported to be in phase I or II clinical trials (Table 1). Among these, alnespirone (Servier, phase II) and binospirone (Hoechst Marion Roussel, phase I) have been the most studied in animals. The former acts as full agonist at both pre- and post-synaptic receptors [14], whereas the latter displays mixed partial agonistic and antagonistic properties [7]. Compared to the compounds described above, alnespirone and binospirone displayed anxiolytic-like effects in animals at lower doses, which ranged from 0.01 to 10 mg/kg [3]. Several other compounds with greater potency than the azaspirones are currently being tested in phase II trials. The full agonists lesopitron (Esteve) [15] and MKC-242 (Mitsubishi) [16] appear to be particularly promising as they display anxiolytic-like activity over a wide dose range, with minimum dose levels in the microgram range [16,17]. Other compounds currently in phase I development are the 5-HT_{1A} receptor antagonist S-15535 (Servier) and the 5-HT_{1A} agonist U-93385 (Pharmacia & Upjohn). The former reduced anxiety-related reactions in several species including rats, mice and pigeons at doses ranging from 0.01 to 40 mg/kg [18], while studies with U-93385 showed that the drug elicited anxiolytic-like effects in rats and mice in the dose range 3 to 10 mg/kg [19]. A few compounds not yet tested in clinical trials have been released recently. Of these, the 5-HT_{1A} receptor antagonist WAY-100135 (Wyeth-Ayerst) has been the subject of the most intense investigation. However, the drug displayed weak anxiolytic-like activity in mice and failed to reduce anxiety-related responses when administered to rats [3]. Two 5-HT_{1A} receptor full agonists S-14506 (Servier) and S-14671 (Servier) show anxiolytic-like activity at very low doses (0.6 µg/kg) in a pigeon conflict model. However, both drugs were inactive in the elevated plus-maze exploration model in rats [20]. Development of S-14506 has been discontinued. Finally, not much is known about the anxiolytic-like potential of SDZ-216-525 (Novartis), a recently disclosed 5-HT_{1A} receptor antagonist from Sandoz; however the drug reduced anxiety-related reactions of mice exposed to the light/dark exploration model [21].

Behavioral effects of 5-HT_2 receptor antagonists

The evidence of an involvement of 5-HT_2 receptors in anxiety has arisen mainly from studies with the methylenepiperazine ritanserin. The compound is described as a non-selective 5-HT_2 receptor antagonist [22] and is reported to be in phase III clinical trials. Evidence for its anxiolytic effects has been inconclusive so far [23]. Similar negative findings have emerged from preclinical studies where ritanserin was found to elicit anxiolytic-like effects in only 40% of the studies [3]. Other non-selective 5-HT_2 antagonists which have been extensively studied in animals are mianserin and ketanserin. Like ritanserin, both compounds exhibited anxiolytic-like effects in less than half of the relevant investigations [3]. Since these agents are extremely non-selective for the 5-HT_2 receptor subtypes, each displaying high affinity for 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} sites as well as for other neurotransmitter receptors [24], it was suggested that these highly variable drug effects could be explained on the basis that not all 5-HT_2receptor subtypes may be involved in the modulation of anxiety or even that they play opposing roles [25]. As a consequence, several selective 5-HT_2 receptor-subtype antagonists have been identified and preliminary behavioral investigations have provided evidence of an anxiolytic-like action in animals. For example, it was shown that the 5-HT_{2B} agonist BW-723C86 (SmithKline Beecham) and the 5-$HT_{2B/2C}$ antagonists SB-200646A (SmithKline Beecham) and SB-206553 (SmithKline Beecham) produced anxiolytic-like effects in conflict models in rats and in marmosets [26-28]. However, these effects were less pronounced in terms of magnitude than those of the benzodiazepine anxiolytic chlordiazepoxide.

Behavioral effects of 5-HT_3 receptor antagonists

5-HT_3 receptor antagonists have been introduced into clinical practice as anti-emetic agents [29]. They are notably used in the prevention of radiation- or chemotherapy-induced nausea and vomiting [30]. Apart from this main action, it has been suggested that 5-HT_3 antagonists may have anxiolytic properties [31]. Most studies have focused on the behavioral effects of ondansetron which was launched as an anti-emetic [32]. Several clinical investigations have been carried out with this drug but no convincing evidence of anxiolytic activity has yet been found [33]. In animal studies, ondansetron displayed anxiolytic-like activity in 63% of cases. Importantly, positive effects were mainly observed in exploration models [3]. Taken together with the clinical findings, this observation led to the suggestion that exploratory tests may be sensitive to a behavioral effect other than an anxiolytic action [34]. This underlines the importance of using conflict models in addition to exploratory tests when the activities of newly released drugs are investigated.

Among the newer 5-HT_3 receptor antagonists, itasetron (Boehringer Ingelheim) has been the most extensively studied in anxiety models. However, only three out of eleven experiments revealed that the drug produced anxiolytic-like responses [3]. Of much greater potential interest are the results obtained with the 5-HT_3 antagonists VA-21B7 (Vita) and WAY-100289 (Wyeth-Ayerst),

although the development status of WAY-100289 is unclear. These compounds reduced anxiety-related reactions in both conflict and exploratory models [35,36]. Finally, positive results have been obtained with the 5-HT_3 antagonists alosetron (Glaxo Wellcome) and RS-42358 (Roche Bioscience) [37]. However, these findings must be approached with caution as only exploratory models were used.

Behavioral effects of 5-HT re-uptake inhibitors (SRIs)

Although originally developed as antidepressants [38], SRIs have been used successfully in the clinical management of several anxiety disorders including panic attacks [39], social phobia [40] and obsessive-compulsive disorders [41]. This clinical efficacy contrasts with the data obtained in animal models of anxiety. For instance, it is noteworthy that imipramine and the selective SRI fluoxetine failed to show evidence of anxiolytic-like action in 70% of the studies. Instead, 20% of the cases revealed opposite effects [3]. However, it is important to note that negative findings were obtained mainly after acute treatment, indicating that repeated administration is required to produce anxiolytic-like effects. These findings concur with the clinical observation of a transient increase in anxiety in some patients at the beginning of treatment with SRIs [42].

Among the newer and pre-marketed SRIs, only duloxetine (Eli Lilly) and cericlamine (Jouveinal) are presently being evaluated in patients with anxiety disorders. However, neither animal nor clinical data on their efficacy against anxiety-related responses have yet become available.

Behavioral effects of 'mixed' compounds

On the basis of the suggestion that pharmacological interactions of drugs combining 5-HT_{1A}, 5-$HT_{2A/2C}$ and/or 5-HT re-uptake inhibitor properties might increase therapeutic response [20], several compounds with 'mixed' profiles have been investigated. Among these, much attention has been given to drugs combining 5-HT_{1A} agonistic/antagonistic and 5-$HT_{2A/2C}$ antagonistic properties. Adatanserin (American Home Products) is currently in phase II clinical trials. In animal studies, the compound produced anticonflict effects that were inferior to those of selective 5-HT_{1A} receptor agonists [43]. The preclinical results obtained with FG-5893 (Pharmacia & Upjohn), HT-90B (Chugai) and S-21357-1 (Servier) are much more promising. The drugs displayed potent anxiolytic-like properties and, at least in the cases of HT-90B and S-21357-1, appear to show greater efficacy than selective 5-HT_{1A} or 5-HT_2 ligands [44,45].

Merck KGaA has reported the results of EMD-68843 (Merck KGaA), a compound combining 5-HT_{1A} agonistic and 5-HT re-uptake inhibitor properties. The drug displayed anxiolytic-like activity in the rat ultrasonic vocalization test. These effects were comparable to those of the 5-HT_{1A} partial agonist buspirone, but were greater than those of the selective SRI, fluoxetine [46].

Conclusion

It is somewhat surprising to note that after more than thirty years of preclinical research relating 5-HT and anxiety, only one direct 5-HT-acting compound, buspirone has been launched as an anxiolytic agent. In addition, only SRIs have been successfully used in the chronic treatment of panic attacks and obsessive-compulsive disorders. Nevertheless, interest in this research area has not decreased and novel 5-HT-modulating agents are still being developed. Much attention has focused on the behavioral effects of selective 5-HT_{1A} receptor ligands, but interest in drugs combining 5-HT_{1A}, 5-HT_2 and/or 5-HT re-uptake inhibitor properties is increasing, although it is not yet clear whether their therapeutic potential is superior to that of selective 5-HT compounds. Clinical data on the efficacy of selective 5-HT_2 and 5-HT_3 receptors antagonists in anxiety are lacking. However, animal studies seem to indicate that these drugs are of limited therapeutic utility in anxiety disorders.

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