Azapirones for the treatment of anxiety – an overview

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ABSTRACT

Anxiety disorders belong to the most common psychiatric diagnosis. Over the years, benzodiazepines were considered the gold standard for pharmacological treatment of anxiety. They are effective anxiolytics, but unfortunately the long-term use of benzodiazepines is accompanied by many adverse events. An alternative to classical anxiolytics is a relatively new class of psychotherapeutic drugs – azapirones. They are 5-HT₁₅ partial agonists commonly used in the treatment of generalized anxiety disorder and as augmentation for SSRI in social anxiety disorder and depression. Due to the high ratio of benefits to risk, azapirones are extensively studied for their use in other disease entities. The aim of this article was to overviewed current information on azapirones. Their history of development, mechanism of action, pharmacokinetics, interactions, clinical use and their role in the modern pharmacotherapy of anxiety.

Keywords: azapirones, buspirone, gepirone, ipsapirone, tandospirone, anxiety disorder
1. INTRODUCTION

Anxiety disorders are one of the most common mental complaints in the world. They can self-exist, however, their presence in the image of other psychological illness is very often noted, among others in depression [61]. According to epidemiological studies, it is estimated that over 42% of all depressive disorders are mixed anxiety-depressive syndromes, and in the case of over 19%, depression is described with coexisting anxiety [53].

Moreover the presence of anxiety in the course of depressive disease translates into greater severity of symptoms, stronger impairment of psychosocial functions and less optimistic prognosis [27]. It is associated with a weaker response to treatment and a higher risk of suicidal episodes [14].

The coexistence of anxiety with other psychological illness and numerous somatic and autonomic symptoms – especially in the case of panic disorder – make correct diagnosis and treatment of anxiety disorders still pose a challenge for modern medicine [46]. Also from a pharmacological point of view, the treatment of anxiety disorders is problematic. Although drugs used in the treatment of anxiety constitute a large group of agents with different mechanisms of action, there is still a lack of complex preparations. Most of the drugs used are not very specific and often have a more sedation-oriented effect than anxiolytic properties. Others, despite their higher specificity (e.g. benzodiazepines) generate problems of addiction and tolerance [47, 57].

A relatively new class of psychotherapeutic drugs - azapirones – may be the answer to the problem of the proper pharmacotherapy of anxiety. Azapirones are a great advance in the design of drugs with anxiolytic and antidepressant properties. Due to the high ratio of benefits to risk, azapirones are widely used and examined in the treatment of anxiety, mixed anxiety-depressive disorder, as well as other psychiatric diseases related to dysfunctions of serotonin mechanisms [7].

2. MATERIALS AND METHODS

A literature search was performed using PubMed, Scopus, Web of Science, Google Scholar databases. The following terms were searched: “azapirones”, “buspirone”, “gepirone”, “ipsapirone”, “tandospirone”, “(anxiety OR anxiety disorder OR anxiety treatment) AND azapirones” and limited to the English or Polish language.

2. 1. History of development

First attempts to treat anxiety disorders have their origins in ancient times. Over the centuries, anxiolytic drugs have gradually evolved from simple, non-selective substances like alcohol, opioids or bromides, through barbiturates and meprobramat, to a breakthrough in 1958 - the patenting of the first benzodiazepine, i.e. chlordiazepoxide.

This discovery introduced pharmacotherapy of anxiety in the era of modern medicine, and benzodiazepines themselves became one of the most frequently prescribed drugs in history. With the popularity of benzodiazepines, more and more problems related to their use have begun to be revealed: tolerance, addiction, mass consumption - resulting from self-medication - leading to numerous dangerous and often fatal overdoses [30, 32].
This phenomenon forced intensified attempts to search for and design new substances with anxiolytic activity. The FDA (Food and Drug Administration) approval of a new drug for the treatment of GAD (General Anxiety Disorder) – buspirone – in 1986, marked a new age of psychotherapeutic drug therapy [13]. Among other substances belonging to the class of azapirones, alphabetically, alnespirone, binospirone, enilospirone, eptapirone, gepirone, ipsapirone, revospirone tandospirone, umespirone, zalospirone can be mentioned [7, 23]. They remain at various stages of development or research on them has been abandoned. The three most promising agents – gepirone, ipsapirone, tandospirone (Table 1.) – are undergoing clinical trials for the treatment of GAD [58]. Nowadays, tandospirone is also registered in China as an antidepressant and anxiolytic drug [3].

**Table 1.** Structures of azapirones. Modified from: [58]

<table>
<thead>
<tr>
<th>R</th>
<th>Name of compound</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="structure1.png" alt="Buspirone structure" /></td>
<td>Buspirone</td>
</tr>
<tr>
<td><img src="structure2.png" alt="Gepirone structure" /></td>
<td>Gepirone</td>
</tr>
<tr>
<td><img src="structure3.png" alt="Ipsapirone structure" /></td>
<td>Ipsapirone</td>
</tr>
</tbody>
</table>
2. 2. Pharmacotherapy of anxiety disorders

From a pharmacological point of view, the treatment of anxiety disorders can be characterized according to two main directions of action of used drugs. One of them is the agonistic effect of ligands on the GABA-ergic system – more precisely on the GABA\(_A\) receptors [45]. The most well-known representatives of this mechanism are benzodiazepines being the gold standard for the treatment of anxiety disorders. The second direction of action of anxiolytics is affecting the functioning of the serotonin system. This mechanism underlies therapeutic efficacy, among others azapirone anxiolytics and a variety of antidepressant drugs [23].

2. 3. Mechanism of action

The exact mechanism of the anxiolytic action of azapirones still remains unclear. However, it is known, that it results from the partial agonism toward the serotonin 5-HT\(_{1A}\) receptor [26]. These receptors belong to the G protein coupled receptors (GPCR) superfamily. Their activation inhibits adenylyl cyclase and decreases the amount of cAMP (3’,5’-cyclic adenosine monophosphate) thanks to the G\(_i\) and G\(_o\) proteins (Figure 1.) [25]. The highest concentration of 5-HT\(_{1A}\) receptors in human body is observed in the limbic areas of the brain (including hippocampus, amygdala, lateral septum) and raphe nuclei. In smaller amounts, they are also located in the cortical areas (especially prefrontal cortex and entorhinal cortex), thalamus, hypothalamus and basal ganglia (e.g. in the striatum) [41].

5-HT\(_{1A}\) receptors exist as both presynaptic autoreceptors as well as postsynaptic heteroreceptors. As autoreceptors, they are located on the bodies and dendrites of serotonin neurons in the area of the raphe nuclei. They inhibit the activity of the system, causing suppression of endogenous serotonin secretion into the synaptic space by means of negative feedback. The effect is a weakening of the transmission in serotonin neurons. Due to this mechanism, 5-HT\(_{1A}\) receptors control the general tone of serotonin activity [1, 9]. Postsynaptic 5-HT\(_{1A}\) receptors (heteroreceptors) are located in the terminal nerves of the CNS. They regulate the sensory, motor, autonomic and psychoemotional processes. Their stimulation causes an increase in the activity of serotonin neurons, while inhibiting the transmission in other neurons, in different areas of the brain (e.g. hippocampus or cerebral cortex) [1].

Numerous scientific studies suggest that the insufficient activity of 5-HT\(_{1A}\) receptors plays a key role in the pathomechanism of anxiety. In studies conducted on knockout mice – with an inactivated gene coding the 5-HT\(_{1A}\) receptor – it was found that animals with
a receptor deficiency, have a greater tendency to avoid the fearful environment and stressful situations compared to mice with an intact receptor [42].

Also observations conducted on patients suffering from anxiety disorders confirm the participation of 5-HT$_{1A}$ receptors in the etiology of anxiety. Nash and colleagues found that the positron emission tomography (PET) scan of untreated patients with panic disorder shows significant changes in the 5-HT$_{1A}$ receptor domain. In comparison with healthy volunteers, both presynaptic and postsynaptic 5-HT$_{1A}$ receptor binding was reduced in untreated patients. The most significant reductions has been observed in the raphe, orbitofrontal cortex, temporal cortex and amygdala [38].

Azapirones, in the presynaptic 5-HT$_{1A}$ autoreceptors, behave as total agonists. They stimulate the activity of 5-HT$_{1A}$ presynaptic autoreceptors, and thus inhibit the release of endogenous serotonin from synaptic terminals. However, with long-term administration of azapirones, down-regulation (desensitization) of these receptors and enhanced serotonin release occurs. In the case of postsynaptic 5-HT$_{1A}$ heteroreceptors, azapirones are partial antagonists, i.e. they act as antagonists when serotonin levels at receptor area are high, and as agonists when serotonin levels are low [22, 51]. Stimulation of postsynaptic 5-HT$_{1A}$ heteroreceptors in corticolimbic structures causes an increase in the activity of monoamine system and, as a result, produces anxiolytic and antidepressant-like effect. Additionally, these receptors have a modulatory effect on other neurons (e.g. glutamatergic) in various brain regions, which can also contribute to this effect [1].

**Figure 1.** 5-HT$_{1A}$ partial agonist (buspirone) mechanism of action. Modified from: [43]

Besides the effects on serotonin mechanisms, scientific reports are increasingly focusing on two alternative mechanisms of action of azapirones. One of them is the dopaminergic theory of azapirones. Buspirone is an antagonist of dopamine receptors with high affinity for
the D3 and D4 receptor and lower for D2 [28]. Recent studies on animal models indicate the involvement of dopamine D3 receptors in the occurrence of anxiety behavior [12, 37]. The above results may suggest that at the base of the anxiolytic effects of buspirone lies its affinity for the D3 receptor. Another alternative mechanism of action of azapirones is based on their affinity for adrenergic receptors. The α2 adrenergic receptors located on serotonergic neurons modulate the release of serotonin from synaptic terminals [49]. Buspirone as an antagonist of α2 adrenergic receptors increase secretion of endogenous serotonin [20].

2. 4. Pharmacokinetics

Azapirones are generally administered orally and rapidly absorbed, with a very short half-lives of approximately 1-3 hours. As a result, they must be administered several times a day (e.g. buspirone and tandospirone – 3 times daily) [17, 33]. The exception is umespirone with a long duration of action up to 23 hours [24]. Unfortunately, umespirone has not been commercialized, but research is currently ongoing on the development of extended-realease formulation of buspirone [48].

Azapirones are metabolized mainly in the liver and excreted in urine and feces. Most azapirones including buspirone, gepirone, ipsapirone, tandospirone have common metabolite 1-(2-pyrimidinyl)-piperazine (1-PP). 1-PP has 5-HT1A partial agonist and α2-adrenoceptor antagonist activity, but mostly it is associated with the occurrence of side effects [34, 60].

2. 5. Clinical use

To date, the main and only registration indication for azapirones is GAD. At the same time, buspirone still remains the only one (apart from tandospiron, registered only in Asian countries) commercially used azapirone. Its use in the treatment of GAD is often questioned, however, numerous studies confirm its effectiveness in eliminating anxiety symptoms [8, 15, 59]. It is also effective in the treatment of GAD with coexisting depressive symptoms [19, 50]. In addition to GAD, azapirones have a wide range of so-called off-label use. Buspirone is used, among others, to potentiate the SSRI (selective serotonin reuptake inhibitors) action in the treatment of social anxiety disorder [35]. Azapirones also demonstrate antidepressant efficacy, both in studies conducted on rodents as well as in human clinical trials [4, 5, 29, 44]. Unfortunately, their usefulness in this context is limited and occurs only in the case of milder forms of depression. Nevertheless, they are commonly employed as an augmentation of SSRI [52]. Buspirone can also be effective in the treatment of panic disorder [26], functional dyspepsia [21], ADHD (attention-deficit hyperactivity disorder) [10], ADD (attention deficit disorder) [40] or even alcoholism [6, 31]. However, in these cases the results are not clear, so further studies are needed. Azapirones can also be effective as augmentation agent in treatment of schizophrenia. Studies on buspirone and tandospirone have shown that they may have a possible benefits in enhancing some types of cognitive performance in patients suffering from this mental disorder. [55, 56].

2. 6. Interactions

Buspirone turns out to be relatively safe in combination with a wide variety of different agents. Most common interaction of buspirone is observed with MAO (monoamomino oxidase) and is responsible for occurrence of hypertension. Significant adverse interaction have also been observed during concomitant administration with cyclosporine, haloperidol,
clomipramine and disulfiram. Buspirone can be safely used with wide range of antidepressants, hypertensives, H₂-blockers, anticonvulsants and anti-diabetic medications. Furthermore comparing to benzodiazepines buspirone does not exhibit serious interactions with alcohol [33, 54, 60].

2.7. Comparison to benzodiazepines

Azapirones are generally well tolerated class of drugs with very wide therapeutic index and small range of side effects. Thus, with relatively safe profile, buspirone can be an alternative to other anxiolytics with a lower ratio of benefits to risk, such as benzodiazepines. The most common side effects of buspirone are: dizziness and lightheadedness, headache, nervousness, nausea, diarrhea, paresthesia, excitation and sweating [11, 16]. Compared to benzodiazepines (Table 2.), patients treated with buspirone are less likely to experience fatigue and weakness and less frequent depressive episodes [39]. In addition, buspirone does not induce sedation and has no addiction potential. Therefore no withdrawal symptoms or rebound anxiety following discontinuation occurs. Buspirone also does not affect cognitive performance and driving skills and does not interact with alcohol [16].

However, the results of the studies are not clear whether azapirones are as effective as benzodiazepines in the treatment of GAD [8, 18, 36]. In addition, in the case of patients previously treated with benzodiazepines, buspirone may prove insufficiently effective. The reason for this phenomenon is unknown [8, 18]. Moreover, buspirone has a slow onset of action with latency around 1-3 week [16]. For this reason it is not recommended as a first-line agent in treatment of GAD [2].

Table 2. Comparison of clinical effects of azapirones and benzodiazepines
(+ effect occurs; – effect does not occur)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Azapirones</th>
<th>Benzodiazepines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast onset of action</td>
<td>- (1-3 weeks)</td>
<td>+</td>
</tr>
<tr>
<td>Direct effect on anxiety</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Antidepressant effect</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Anticonvulsant effect</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Hypnotic effect</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Sedative effect</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Myorelaxant effect</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Amnestic effect</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Impact on panic attacks</td>
<td>-</td>
<td>+ (alprazolam)</td>
</tr>
</tbody>
</table>
Strong impact on psychomotor functions | - | +
--- | --- | ---
Impact on respiratory center | - | +
--- | --- | ---
Interaction with alcohol | - | +
| (potentiation of action)
--- | --- | ---
Paradoxical stimulant effects | - | +
--- | --- | ---
Withdrawal syndrome after discontinuation of treatment | - | +
--- | --- | ---
Addictive potential | - | +

3. CONCLUSIONS

Azapirones are a popular and widely used class of drugs in the treatment of anxiety disorders. Numerous scientific studies confirm effectiveness of buspirone in the treatment of GAD. It also turns out to be effective as an augmentation of SSRI in the treatment of social anxiety disorder and depression. Due to its relatively safe pharmacological profile and few adverse effects, buspirone is extensively studied in its use in other disease entities, such as: panic disorder, functional dyspepsia, ADHD and ADD, alcoholism or schizophrenia. Despite many advantages, buspirone does not meet all expectations, such as the lack of direct antidepressant action or in some cases debatable anxiolytic action. For this reason, new compounds from the class of azapirone derivatives are persistently designed and tested. Unfortunately, today buspirone still remains the only azapirone used on a wider scale.

References


