The action of aripiprazole and brexpiprazole at the receptor level in singultus

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DOI:10.31083/j.jin.2021.01.273
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Submitted: 10 September 2020 Revised: 06 December 2020 Accepted: 14 December 2020 Published: 30 March 2021

The hiccup (Latin, singultus) is an involuntary periodic contraction of the diaphragm followed by glottic closure, which can be a rare side effect of aripiprazole. In contrast to the structurally closely related aripiprazole, brexpiprazole was not associated with this particular adverse drug reaction. Having two very similar drugs that differ in their ability to induce hiccups represents a unique opportunity to gain insight into the receptors involved in the pathophysiology of the symptoms and differences in clinical effects between aripiprazole and brexpiprazole. The overlap between maneuvers used to terminate paroxysmal supraventricular tachycardia and those employed to terminate bouts of hiccups suggests that activation of efferent vagal fibers can be therapeutic in both instances. Recent work seems to support a pivotal role for serotonin receptors in such vagal activation. It is unlikely that a unique receptor-drug interaction could explain the different effects of the examined drugs on hiccup. The different effect is most likely the consequence of several smaller effects at more than one receptor. Brexpiprazole is a highly affine (potent) α2C antagonist and, therefore, also an indirect 5-HT1A agonist. In contrast, aripiprazole is a partial 5-HT1A agonist (weak antagonist) and an HT3 antagonist. Activation of 5-HT1A receptors enhances vagal activity while HT3 blockade reduces it. Vagus nerve activation is therapeutic for hiccups. A definitive answer continues to be elusive.

Keywords
Neuropharmacology; Hiccup; Serotonin; Aripiprazole; Brexpiprazole; Affinity constant

1. Introduction
Hiccup (Latin, singultus) is caused by an involuntary periodic contraction of the diaphragm followed by the glottis’s closure. The inspired air meeting a closed glottis causes the familiar hiccup sound. Hiccupping lasting longer than four weeks is considered chronic. Treatment resistance (obstinate hiccup) is defined as a lack of response to many (mostly three) successive pharmacological treatments attempt. Generally, the longer the hiccupping duration, the less amenable it will be to interventions [1].

Singultus is not a disease but a symptom. The most commonly encountered hiccup is that of idiopathic origin. While many drugs have been tried off-label in hiccup therapy, chlorpromazine is the only FDA approved drug for this purpose. In contrast, only a few drugs (benzodiazepines, barbiturates, alcohol, and steroids) and the phenyl-piperazine atypical antipsychotic aripiprazole are well-established hiccup inducers [1].

Since the initial observation made by Behere [2] that aripiprazole can induce hiccups (in his case, associated with hypotension), an abundance of reports on hiccups associated with aripiprazole treatment emerged [3–11], and on persistent hiccups associated with switching antipsychotic treatment to aripiprazole [12–15].

More recently, brexpiprazole was introduced into clinical practice [16]. In contrast to the structurally closely related aripiprazole, brexpiprazole was not associated with this particular adverse drug reaction. Having two very similar drugs that differ in their ability to induce hiccup represents a unique opportunity to gain insight into the receptors involved in the symptom’s pathophysiology.

To identify the critical difference responsible for the discrepancy, we performed a literature search (PubMed and public domain sources) and retrieved and compared the PK/PD data and properties of the two piperazine antipsychotics at serotoninergic, alpha2-adrenergic and dopaminergic receptors.

While aware of the limitations of comparing receptor affinities/intrinsic activity values—even more so when obtained from different sources using different methodologies—(as they have considerable confidence intervals) and inferring biological effects based on such data, it is currently the only practical available option for our analysis [17, 18].

2. Methods
To identify the critical difference responsible for the discrepancy, a literature search (PubMed and public domain sources) was performed, and pharmacokinetics and pharmacodynamic (PK/PD) data/properties of the two piper-
azine antipsychotics at serotoninergic alpha2–adrenergic and dopaminergic receptors retrieved and compared. Due to the limited number of publications containing pharmacokinetic and or pharmacodynamic details on aripiprazole and brexiprazole, no filters were applied.

As a matter of terminology - as used by us-when comparing Kᵢ values of the two drugs, very (strong) high affinity implies subnanomolar Kᵢ values, high-affinity Kᵢ between 1 and 10 nM, moderate Kᵢ between 10 and 50 nM, low affinity is Kᵢ between 50 and 100 nM and very (weak) low affinity for Kᵢ higher than 150 nM. For Kᵢ values above 90% of the therapeutic plasma range (700 nM for aripiprazole and 300 nM for brexiprazole), no effect via the respective receptor is assumed. The inhibition constant (Kᵢ) is calculated based on the following: Kᵢ = IC₅₀ for noncompetitive inhibition, Kᵢ = IC₅₀/2 for competitive inhibition, and Kᵢ values range from IC₅₀ to IC₅₀/2 for mixed inhibition, according to the equation [19]: Kᵢ = IC₅₀/[1 + ([L]/Kd)] where [L] is the concentration of ligand (nM), and Kd is the affinity constant (nM).

For comparison purposes Kᵢ ratios are given as Kᵢ aripiprazole/Kᵢ brexiprazole, i.e., [Kᵢ (ARI/BREX)]; a value > 1 indicates lower affinity of aripiprazole for the respective receptor while a value < 1 indicates higher affinity of aripiprazole for the respective receptor. Divergent or significantly different effects are assumed when the ratio is either > 10² or < then 10⁻². The same applies when only one of the drugs has a Kᵢ within the therapeutic range [22]. Kᵢ is used to describing the binding affinity that a molecule has for an enzyme or receptor. The half-maximal inhibitor concentration IC₅₀ is more reflective of the inhibitor’s functional strength, but both factors in the drug's concentration inhibit the activity. Efficacy is the relationship between receptor occupancy and the ability to initiate a response. As a matter of terminology - as used by us-when comparing Kᵢ (binding affinity constant) values of the two drugs, very (strong) high affinity implies subnanomolar Kᵢ values, high-affinity Kᵢ between 1 and 10 nM, moderate Kᵢ between 10 and 50 nM, low affinity is Kᵢ between 50 and 100 nM and very (weak) low affinity for Kᵢ higher than 150 nM. For Kᵢ values above 90% of the therapeutic plasma range (700 nM for aripiprazole and 300 nM for brexiprazole), no effect via the respective receptor is assumed. The brain aripiprazole concentration is approximately 0.6-0.9 of the respective plasma concentrations [21], while brexiprazole is 0.2-0.4 [20]. These ratios are difficult to interpret, as they do not compare Cₘₐₓ plasma with Cₘₐₓ brain.

The abstracts of the 60 documents (search 2 and 4) were evaluated by two of the authors (GAP & EA) for the likelihood the paper containing relevant pharmacokinetic and pharmacodynamics (pK/pD) data (affinity, IC₅₀, EC₅₀, receptor occupancy). The consensus papers were mined for the targeted data. To complement the information thus obtained, a series of databases and other public domain publications (European Medicines Agency (EMA), 2018; Drugs FDA; Lundbeck; American Psychiatric Association; PubChem Database) were also consulted. Sources are cited wherever they are used.

3. Results

3.1 Serotonin (5-HT) receptors

5-HT₁A (Kᵢ, 5-HT ≈ 2): Brexiprazole, despite an affinity one order of magnitude higher ([Kᵢ(ARI/BREX)] ≈ 1.7/0.12 ≈ 14) than aripiprazole, displayed comparable receptor occupancy and an only slightly lower efficacy [Emax expressed as a percentage of the effect of serotonin = 0.6 BREV vs. 0.7 ARI] [23]. Both drugs are less efficacious than the endogenous neurotransmitter serotonin (Eₘₐₓ ≈ 1), thus acting as partial agonists. The two drugs have very similar effects via this receptor, even though some argue that brexiprazole is a full 5-HT₁A receptor agonist [24, 25] (Table 1).

5-HT₁B (Kᵢ, 5-HT ≈ 4): While aripiprazole is unlikely to significantly affect this receptor (Kᵢ outside of the therapeutic range, brexiprazole will act as an antagonist. One can speculate that brexiprazole as an antagonist will have some vasodilating effect (Table 1).

5-HT₂A (Kᵢ, 5-HT ≈ 12): The effects of brexiprazole and aripiprazole at 5-HT₂A are measured via studying DOI (2,5-dimethoxy-4-iodoamphetamine)-induced head twitches (mediated via 5-HT₂A): brexiprazole and aripiprazole inhibited DOI-induced head twitches; maximum responses (Mean ± S.E.M.) for brexiprazole and aripiprazole were; 99 ± 0.9, and 91 ± 3.6, respectively. Brexiprazole, despite an affinity about one order of magnitude higher ([Kᵢ(ARI/BREX)] ≈ 3.4/0.47 ≈ 7) than aripiprazole, displayed comparable 2A receptor occupancy [23]. As with all atypical antipsychotics, both drugs act at this receptor as antagonists. The two drugs have similar effects via this receptor [26]. Thus, it is unlikely that interaction with this receptor might explain the different ADR profile of the two drugs (Table 1).

5-HT₂B (Kᵢ, 5-HT ≈ 9): Brexiprazole, despite a lower 2B affinity than aripiprazole ([Kᵢ(ARI/BREX)] ≈ 0.36/1.9 ≈ 0.2) displayed comparable IC₅₀ ≈ 10-15 nM [16, 23, 27].
While $K_i$ is used to describing the binding affinity that a molecule has for an enzyme or receptor.

The half-maximal inhibitory concentration $IC_{50}$ is more reflective of the inhibitor’s functional strength, but both factors in the drug’s concentration inhibit the activity. The drugs act at this receptor as antagonists/inverse agonists and have similar effects via this receptor. Thus, it is unlikely that interaction with this receptor might explain the difference in ADR profile of the two drugs (Table 1).

### Table 1. The affinity ratio between Aripiprazole and Brexpiprazole $K_i^{(ARI}/BREX)$ and effect at different serotonin receptors and transporter.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>ARI $K_i$ nM</th>
<th>BREX $K_i$ nM</th>
<th>$K_i^{(ARI}/BREX)$</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT$_1$A</td>
<td>1.3 [23]</td>
<td>0.12 [23]</td>
<td>14</td>
<td>partial agonism</td>
</tr>
<tr>
<td>5-HT$_1$B</td>
<td>830 [27]</td>
<td>32 [23]</td>
<td>26</td>
<td>antagonism</td>
</tr>
<tr>
<td>5-HT$_1$D</td>
<td>68 [27]</td>
<td>Not available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT$_1$E</td>
<td>8000 [27]</td>
<td>Not available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT$_2$A</td>
<td>4.7 [23]</td>
<td>IC$_{50}$ 6.5</td>
<td>10</td>
<td>antagonism</td>
</tr>
<tr>
<td>5-HT$_2$B</td>
<td>0.36 [58]</td>
<td>1.9 [23]</td>
<td>0.2</td>
<td>antagonism/inverse agonism</td>
</tr>
<tr>
<td>5-HT$_2$C</td>
<td>15 [27]</td>
<td>34 [27]</td>
<td>0.4</td>
<td>antagonism</td>
</tr>
<tr>
<td>5-HT$_3$</td>
<td>630 [27]</td>
<td>Not available</td>
<td></td>
<td>Possibly divergent; only ARI</td>
</tr>
<tr>
<td>5-HT$_5$</td>
<td>1240 [27]</td>
<td>140$^a$</td>
<td>8.9</td>
<td>possibly divergent; only BREX</td>
</tr>
<tr>
<td>5-HT$_6$</td>
<td>570 [27]</td>
<td>60 [23]</td>
<td>3.6 - 9.5</td>
<td>weak antagonism</td>
</tr>
<tr>
<td>5-HT$_7$</td>
<td>219 [59]</td>
<td>39 [27]</td>
<td>3.7</td>
<td>weak partial agonism</td>
</tr>
</tbody>
</table>

$IC_{50}$: serotonin transporter 95 (IC$_{50}$) 29 (IC$_{50}$) 3.3 $IC_{50}^{(ARI}/BREX)$ |


Brexpiprazole $K_i$ at this receptor is negligible with a $K_i$ of 1.240 ± 280 nM, above the upper limit of the therapeutic plasma range [27]. Brexpiprazole $K_i$ of 140 nM$^2$. The only brexpiprazole likely has an effect mediated by this receptor (Table 1).

### 5-HT$_2$C ($K_i$ 5-HT := 5)

Binding affinity of brexpiprazole at the 2C receptor was lower than that of aripiprazole: $[K_i^{(ARI}/BREX)] \approx 15/34 \approx 0.4$. Despite that, the two drugs showed similarly low efficacies ($E_{max} \approx 10\%$) compared with serotonin. Both drugs act as weak partial agonists, de facto antagonists [26, 27] (Table 1).

### 5-HT$_3$ ($K_i$ 5-HT := 200)

$K_i$ of aripiprazole at this receptor is $K_i$ 630 ± 110 nM [27]. In comparison the endogenous agonist 5-HT has a $K_i$ of 200 nM [28]. No data for brexpiprazole could be found, nor any indication that the drug would interact with this receptor. Only aripiprazole likely has a weak effect mediated via this receptor (Table 1).

### 5-HT$_4$ ($K_i$ 5-HT := 120)

There is no available data suggesting any effect of the two drugs via this receptor.

### 5-HT$_5$ ($K_i$ 5-HT := 200)

Binding affinity of aripiprazole at this receptor is negligible with a $K_i$ of 1.240 ± 280 nM, above the upper limit of the therapeutic plasma range [27]. The affinity of the weak antagonist brexpiprazole is similar to that of serotonin (58 nM), but the receptor occupancy is low at 20-40%. $K_i^{(ARI}/BREX) \approx 3.5$. Both drugs act as weak antagonists (Table 1).

### 5-HT$_6$ ($K_i$ 5-HT := 65)

$K_i$ of aripiprazole $\approx 214$ (reported range from 161 ± 17 [29] to 570 ± 95 nM [27, 29] and 780 [30]). The affinity of the weak antagonist brexpiprazole is similar to that of serotonin (58 nM), but the receptor occupancy is low at 20-40%. $K_i^{(ARI}/BREX) \approx 3.5$. Both drugs act as weak antagonists (Table 1).

### 5-HT$_7$ ($K_i$ 5-HT := 2-8)

The affinity of the endogenous agonist serotonin for the 5-HT$_7$ receptor is (strong) high

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Aripiprazole, a very weak partial agonist with an $E_{\text{max}} < 10\%$ (of 5-HT effect), has a $K_i \approx 39 \text{ nM}$ and a receptor occupancy in the 15-30\% range [27, 31, 32]. Brexpiprazole, a weak partial agonist, has a $K_i$ of 3.7 nM and a receptor occupancy in the 10-56\% range [34]. $K_i^{(\text{ARI}}/\text{BREX)} \approx 10$ (Table 1).

At the 5-HT$_7$ receptor, while aripiprazole has a (weaker) lower affinity than brexpiprazole, both drugs have similar effects (weak partial agonist, de facto antagonist) [26] (Table 1).

SERT ($K_i$ 5-HT $\approx 500$) [35]: Aripiprazole has an IC$_{50}$ for the serotonin transporter $\approx 95$ nM. Brexpiprazole is a SERT inhibitor with an IC$_{50}$ of 29 nM but a low ligand displacement ability (65\% at 10 $\mu$M) [31] (Table 1).

### 3.2 Alpha $\alpha_2$ (α2) adrenergic receptors

Brexpiprazole is a highly affine $\alpha_2$ adrenergic receptor antagonist ($\alpha_{2A}$ $K_i$ 15 nM; $\alpha_{2B}$ $K_i$ 17 nM; $\alpha_{2C}$ $K_i$ 0.59 nM) comparable to mirtazapine ($\alpha_{2A}$ $K_i$ 20 nM; $\alpha_{2B}$ $K_i$ 88 nM; $\alpha_{2C}$ $K_i$ 18 nM) [23, 30]. Aripiprazole has a slightly lower affinity for $\alpha_2$ adrenergic receptors ($\alpha_{2A}$ $K_i$ 74 nM; $\alpha_{2B}$ $K_i$ 100 nM; $\alpha_{2C}$ 37 nM) [30]. $K_i^{(\text{ARI}}/\text{BREX)}$ for the $\alpha_2$-adrenergic receptors is $\alpha_{2A} \approx 5$; for $\alpha_{2B} \approx 6$ while for $\alpha_{2C} \approx 63$. Brexpiprazole has an IC$_{50}$ of 63 nM at $\alpha_2$ receptors [23] (Table 2).

### 3.3 Dopamine (DA) receptors

$D_1$ ($K_i$ DA $\approx 2$-8): Aripiprazole has a $K_i \approx 265$ nM (reported range 200-2500 nM) [19, 27, 29]; brexpiprazole has a $K_i \approx 150\%$. $K_i^{(\text{ARI}}/\text{BREX)} \approx 265/160 \approx 1.7$. Both drugs have similar agonist effects [36, 37] (Table 3).

$D_5$ ($K_i$ DA $< 2$): Aripiprazole has a $K_i \approx 2590 \pm 1350$ nM, well above the upper limit of the therapeutic plasma range [27]. Similar values ($K_i \approx 1.670 \text{ nM}$) have been reported by [38]. For brexpiprazole receptor, occupancy is $\approx 66\%$ at 1 nM (Table 3).

$D_2$ ($K_i$ DA $\approx 12$ ± 4) [39]: Aripiprazole, a partial agonist with an Emax $\approx 60\%$ (of D effect), has a $K_i \approx 0.32$ nM. Brexpiprazole, also a partial agonist, has a $K_i$ 0.3 nM and an Emax $\approx 43\%$. $K_i^{(\text{ARI}}/\text{BREX)} \approx 1$. At the $D_2$ receptor, both drugs have similar effects (partial agonist) (Table 3).

$D_3$ ($K_i$ DA $\approx 3 \pm 1$) [39]: Aripiprazole, a partial agonist with an Emax $\approx 30\%$ (of DA effect), has a $K_i \approx 0.8$ nM. Brexpiprazole, a weak partial agonist, has a comparable affinity ($K_i \approx 1.1$) but a lower intrinsic activity Emax $\approx 15\%$. $K_i^{(\text{ARI}}/\text{BREX)} \approx 0.8$. At the $D_3$ receptor, while both drugs have qualitatively similar effects (partial agonist), aripiprazole has a somewhat higher intrinsic activity [26] (Table 2).

$D_4$ ($K_i$ DA $\approx 6 \pm 2$) [39]: Aripiprazole has a $K_i \approx 44$ nM and an Emax of 20-30\% [40]. Brexpiprazole has a higher affinity $K_i \approx 6$ nM. $K_i^{(\text{ARI}}/\text{BREX)} \approx 7$. Both drugs have a partial agonist effect at this receptor (Table 3).

$D_A$T ($K_i$ DA $\approx 29 \pm 4$) [41]: Brexpiprazole is a negligible inhibitor of the dopamine transporter with a reported IC$_{50}$ $\approx 950$ nM, well above the upper limit of the therapeutic plasma range; the same applies for aripiprazole ($K_i \approx 3220 \pm 660$) [27] (Table 3).

### Discussion

To identify differences that might explain the differential effect of the two drugs on hiccup, the affinities of aripiprazole and brexpiprazole for the various serotoninergic, alpha$_2$ adrenergic and dopaminergic receptors, as well as the respective transporters, were compared. The drugs are very similar in their pharmacodynamics at most receptors. They are generally considered partial agonists at 5-HT$_1A$, and $D_2$ receptors and antagonists at the 5-HT$_2A$ receptors; brexpiprazole has a somewhat lower intrinsic activity at the $D_2$ receptor and acts as a more potent 5-HT$_1A$ agonist and as a stronger 5-HT$_2A$ antagonist [17]. Furthermore, both drugs appear to have additional characteristics beyond partial agonist at $D_2$ receptors, including biased agonism [42, 43]. The term biased agonism (functional selectivity), initially introduced in [44], describes the phenomenon that a ligand preferentially activates one of several signaling pathways. In contrast, another agonist in the same system and acting on the same receptor preferentially activates another pathway.

Both are dopamine system stabilizers, i.e., to have either an agonist or antagonist effect depending on the levels of exogenous dopamine (agonist at high dopamine concentration vs. agonist at low dopamine concentration [42, 43]). Aripiprazole and brexpiprazole function as both a presynaptic $D_2$ agonist and postsynaptic $D_2$ antagonist; furthermore, their partial agonistic activity 5-HT$_1A$ receptor plays a role in modulating among other dopamine releases reviewed by [42]. Effects mediated via the major psychosis relevant receptors (5-HT$_1A$, 5-HT$_2$ and $D_2$) are similar and do not provide in our view the explanation for the appearance of a hiccup with aripiprazole treatment.

Different effects appear possible at the 5-HT$_3$ receptor where aripiprazole has a $K_i$ within the therapeutic plasma concentration and the 5-HT$_1B$- and 5-HT$_5$ receptor where brexpiprazole has a $K_i$ within the therapeutic plasma concentration.

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5-HT3 receptors are the only ionotropic serotonin receptors. 5-HT3 receptors are located (mainly) on sensory vagal nerve endings and play a vital role for vagal afferent input originating from organs cranial to the Cannon-Böhm point (the gastrointestinal tract fewer parts of the colon and rectum, lungs and heart). The central terminals of vagal afferents exhibit 5-HT3 receptors that increase glutamatergic synaptic transmission to second-order neurons of the nucleus tractus solitarius [46]. Experimental compounds with 5-HT3 blocking properties increase the heart rate by decreasing vagal afferent input and efferent output; this is compatible with data showing that 5-HT3 receptors excite vagal afferent neurons by a glutamate-dependent mechanism [47, 48]. Blockade of these receptors by 5-HT3 antagonists (setrons) is used clinically for control of emesis.

A single anecdotal mentioning of the negative impact of setrons on a patient with chronic hiccup was published by one of the authors (GAP) [49]. Some anecdotal reports claim that setrons cause hiccups [15], but overall, the evidence is relatively sparse.

The possibility of aripiprazole affecting this receptor (while the same does not apply to brexipiprazole) is nevertheless intriguing as-if confirmed experimentally- it might explain their differential effect on hiccup. Mechanistically an inhibition of this receptor would be expected to lower vagal afferent output, which is believed to favor hiccup development [50].

5-HT5 receptors (Gi protein-coupled) are virtually unexplored due to a lack of selective ligands [51]. As Glennon [52] points out, “the discovery of a therapeutically useful function for the receptors” is still outstanding. The possibility that brexipiprazole might affect this receptor (while the same does not apply for aripiprazole) cannot be inferred much at this point.

5-HT1B receptors (Gi protein-coupled) are the traditional target of the triptan class of drugs. Triptans act as agonists at 5-HT1B and 5-HT1D receptors at blood vessels and nerve endings in the brain and induce vasoconstriction. The only brexipiprazole has a Ki within the therapeutic range (agonist; vasodilation). The significance or lack thereof is difficult to interpret.

Overall, we failed to identify the one receptor that might explain the different effect of the examined drugs on hiccup; it appears likely that the different effect is the consequence of synergism of several smaller effects at more than one receptor. The most consequential concerning neurotransmitter release is the central alpha2 adrenergic receptor.

Brexipiprazole, similar to mirtazapine, is a highly affine α2 antagonist [α2A Ki 15 nM; α2B Ki 17 nM; α2C 0.59 nM] [17]. Antagonism of the α2- receptors, which function mainly as inhibitory autoreceptors and heteroreceptors, enhances transmitter release and favors neurotransmission, notably central 5-HT1A receptor-mediated. Mirtazapine has been said to be a functional "indirect agonist" of the 5-HT1A receptor [53]. Mirtazapine’s Ki for α2-adrenergic receptors is ≈ 20 nM, while aripiprazole’s Ki for α2 receptors [α2A Ki 74 nM; α2B Ki 100 nM; α2C 37 nM] [30].

Ki(ARI/BREX) for the α2-adrenergic receptors is, therefore, α2A ≈ 5; for α2B ≈ 6 while for α2C ≈ 63. While we postulated divergent or significantly different effects when the ratio is either > 102 or < than 10−2 a Ki(ARI/BREX) ≈ 63 at α2C indicates possibly higher efficacy for brexipiprazole. Oosterhof et al., 2014, 2015 argue that brexipiprazole is a full 5-HT1A receptor agonist, possibly due to a combined α2C antagonist-HT1A agonist effect [24, 25]. Such an effect combination would be quite similar to that seen with the azapirone derivative tandospirone, where tandospirone is an HT1A partial agonist while its primary metabolite (1-

### Table 3. The affinity ratio between Aripiprazole and Brexipiprazole and effect at different dopamine receptors and transporter.

<table>
<thead>
<tr>
<th></th>
<th>Kᵢ (ARI) nM</th>
<th>Kᵢ (BREX) nM</th>
<th>Kᵢ(ARI/BREX) nM</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>1960 [27]</td>
<td>160</td>
<td>265/160 ≈ 1.7</td>
<td>agonism</td>
</tr>
<tr>
<td>D5</td>
<td>2590 [27]</td>
<td>0.32</td>
<td>2590/1111</td>
<td>no effect</td>
</tr>
<tr>
<td>D2</td>
<td>0.32 [60]</td>
<td>0.8-1.6 [23]</td>
<td>0.34/0.3 ≈ 1</td>
<td>partial agonism</td>
</tr>
<tr>
<td>D3</td>
<td>44 [23, 39]</td>
<td>1.1</td>
<td>0.8/1.1 ≈ 0.8</td>
<td>partial agonism</td>
</tr>
<tr>
<td>D4</td>
<td>3220 [61]</td>
<td>6</td>
<td>44/6 ≈ 7</td>
<td>partial agonism</td>
</tr>
<tr>
<td>DAT⁺</td>
<td>950</td>
<td>3.220/950 ≈ 3.4</td>
<td>no effect</td>
<td></td>
</tr>
</tbody>
</table>


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Fig. 1. A schematic illustration showing receptor-drug interaction. 1A. Blue Neuron: $\alpha_{2C}$ adrenergic heteroreceptors control neurotransmitter release (i.e., 5-HT). Once released, 5-HT docks at postsynaptic receptors such as 5-HT$_{1A}$ on the yellow neuron. Activation of presynaptic $\alpha_{2C}$ by the neurotransmitter reduces further release while SERT removes 5-HT from the synaptic cleft. 1B. Activation of presynaptic $\alpha_{2C}$ by the neurotransmitter or drug with agonist effect (green triangle) reduces further release (red arrow). In contrast, the drug with antagonist effect (red triangle) increases neurotransmitter release (green arrow). 1C. The primary metabolite of tandospirone (1-PP) is a highly affine $\alpha_{2C}$ adrenergic antagonist, increasing serotonin release and augmenting postsynaptic effects. Tandospirone is a 5-HT$_{1A}$ partial agonist; the combined effect of drug and metabolite is direct and indirect agonism at 5-HT$_{1A}$ (mirtazapine-like effect). 1D. Brexpiprazole is a highly affine $\alpha_{2C}$ adrenergic antagonist, thus increasing serotonin release and augmenting postsynaptic effects. At the same time, brexpiprazole is also a 5-HT$_{1A}$ partial agonist; the combined effect at the two receptors is direct and indirect agonism at 5-HT$_{1A}$ (mirtazapine-like effect).

pyrimidinyl-piperazine; 1-PP) is a centrally acting, the high-affinity $\alpha_2$-adrenergic antagonist ($K_i \approx 10-40$ nM) [54, 55]. Interestingly, tandospirone was successfully used to treat hiccup [56] (See also Fig. 1).

For an overview of $\alpha_{2C}$ receptors, see the recent review from Brian Harvey’s group [57].

Activation of 5-HT$_{1A}$ receptors enhances vagal activity; therefore, 5-HT$_{1A}$ agonists (brexpiprazole) would be unlikely to favor hiccup development. In contrast, 5-HT$_{1A}$ partial agonists (week antagonists) such as aripiprazole might not offer the same benefit [50].

5. Conclusions

It is unlikely that a unique receptor-drug interaction could explain the different effects of the examined drugs on hiccup. The different effect is most likely the consequence of several smaller effects at more than one receptor. Brexpiprazole is a highly affine (potent) $\alpha_{2C}$ antagonist and, therefore, also an indirect 5-HT$_{1A}$ agonist. In contrast, aripiprazole is a partial 5-HT$_{1A}$ agonist (weak antagonist) and an HT$_3$ antagonist. Activation of 5-HT$_{1A}$ receptors enhances vagal activity while HT$_3$ blockade reduces it. Vagus nerve activation is therapeutic for hiccups. A definitive answer continues to be elusive.

Abbreviations

5-HT, 5-hydroxytryptamine, serotonin; CNS, Central nervous system; DA, Dopamine; DAT, Dopamine transporter; EC$_{50}$, concentration of a drug that gives a half-maximal response (nM); E$_{max}$, concentration of a drug that gives a maximal response (nM); IC$_{50}$, half maximal inhibitory concentration (nM); $K_i$, Inhibitor constant (nM); SERT, Serotonin transporter.

Author contributions

Georg Petroianu: planning and conducting the review, literature search, interpreting the literature, and drafting the manuscript; Eman Alefishat: planning and conducting the review, literature search, interpreting the literature, and drafting the manuscript; Lujain Aloum: literature search, interpreting the literature, and drafting the manuscript; Ovidiu Baltatu: literature search, interpreting the literature, and drafting the manuscript.

Ethics approval and consent to participate

Not applicable.
Acknowledgment
We express our sincere thanks to the reviewers for their instructive comments that improved the final version.

Funding
This research received no external funding.

Conflict of interest
The authors declare no conflict of interest.

Consent for publication
All authors have read and approved the manuscript for publication.

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