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Vortioxetine and aggression

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Summary

Vortioxetine is a new chemical entity licensed for the indication of major depressive disorder. With a complex pharmacological mechanism of action, it modulates neurotransmission within the serotonin system, as do serotonin reuptake inhibitors, but also within a number of other systems which are thought to account for additional effects such as improved cognition. A statistical screening of VigiBase, the WHO global database of individual case safety reports, performed in April 2018 and designed to detect safety concerns reported by patients, highlighted the combination vortioxetine and aggression. Given the multimodal actions of vortioxetine, the strength of the clinical support from the case series, and the evidence for a potential role of serotonin in aggression, there is

adequate support for a potential causal relationship between vortioxetine and aggression. Current product information for vortioxetine does not sufficiently inform patients about the potential of aggression as an adverse effect.

Introduction

Vortioxetine (1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine), a structurally new type of psychotropic medication, is considered to have a multimodal pharmacological mechanism of action. In vitro studies have revealed it to be 5-HT3, 5-HT7, and 5-HT1D receptor antagonist, a 5-HT1B receptor partial agonist, a 5-HT1A receptor agonist, and an inhibitor of the 5-HT transporter. Animal models suggest that it modulates neurotransmission within several systems, predominantly the serotonin but probably also the norepinephrine, dopamine (DA), histamine, acetylcholine, GABA and glutamate systems. This multi-modal activity is thought to be responsible for the differences between vortioxetine and the class of serotonin reuptake inhibitors (SSRIs) with vortioxetine exhibiting additional effects such as increased synaptic plasticity and improved cognitive function.[1]

Vortioxetine was approved for use in the treatment of major depressive disorder in adults in the United States of America (USA) and the European Union (EU) in 2013.

At the time of licensure by the European Medicines Agency (EMA), vortioxetine received a black triangle warning, and the risk management plan included a post-authorisation safety study with an aim to "... further characterise the safety profile of vortioxetine by assessing the frequency of the certain events related to important potential risks in patients treated with vortioxetine."[2]

Aggression is defined as "forceful physical, verbal, or symbolic action which may be appropriate and self- protective or inappropriate; aggression may be directed toward the environment, another person/personality, or toward the self" in the McGraw-Hill Concise Dictionary of Modern Medicine.[3] Aggression can be a symptom of certain psychiatric disorders, and it may complicate non-psychiatric illnesses when patients feel unrecognised or disregarded by the medical system.[4] Within clinical practice there exist a number of related words which are used interchangeably with "aggression", such as "anger", "hostility", or "irritability". The granularity of this medical concept is reflected in the MedDRA dictionary by the existence of a standardized MedDRA query (SMQ) "Hostility/Aggression".

The biological mechanism behind aggression is complex, involving several cortical and subcortical brain networks which are modulated by number of neurotransmitter systems, including monoamines, glutamate, and GABA, and by ion channels.[5,6] The main receptors and enzymes involved in the neurobiology of aggression include serotonin 5-HT1A and 5-HT2A receptors, 5-HT transporters, DA D1 and D2 receptors, DA transporters, 1- and 2-adrenoceptors, the enzyme monoamine oxidase (MAO)-A, the GABA system (GABAA and GABAB receptors and GABA transaminase), the glutamate NMDA and AMPA receptors, and voltage- gated Na+ and Ca2+ channels. A clinical manifestation of aggression can occur as a result of dysfunction at genomic and transcriptional levels, as well as at the level of the synthesis and the metabolism of these various neurotransmitters and their receptors.[7,8]

Reports in VigiBase

Table 1 illustrates the disproportionality of vortioxetine and aggression, as of 30 September 2018.

Table 1. Vigilyze disproportionality value (dataset date: 2018-09-30)

Substance	Reaction (PT)	$N_{observed}$	$N_{expected}$	IC_{025}	IC	$N_{country}$	N_{subst}	$N_{reaction}$
Vortioxetine	Aggression	77	21.52	1.48	1.82	19	8.790	44.299

Based on the overall reporting of adverse reactions for vortioxetine and aggression in VigiBase, the WHO global database of individual case safety reports (ICSRs), the expected value for the number of reports on the combination was 22, while the observed number of reports was 77. The statistical significance of the association is shown by the IC_{025} of 1.48.

The case series

Seventy-six ICSRs reporting the MedDRA preferred term (PT) "aggression" with the use of vortioxetine had been received into VigiBase by 30 August 2018 and were included in this case series review. These reports concerned 45 women, 28 men, with three unknown. Age varied from 15 to 90 years, with a median of 47; age was not provided in 26 reports. The largest number of reports for which age was known was the age group 18-44 years. Reports were primarily received from consumers/non-health professionals (n=41) and physicians (n=23). Reports originated from all continents, including the Americas (USA, Canada), Europe (Austria, Denmark, Czech Republic, the Netherlands, Germany, Finland, Italy, Sweden, France, Norway, Spain, Switzerland, the United Kingdom), Asia (Turkey, Republic of Korea) and Africa (Namibia and South Africa). Twenty-seven of the cases were

reported as "serious" and eighteen reports mention aggression as the only preferred term. The most commonly co-reported adverse drug reactions (ADRs) were irritability (14 reports), suicidal ideation (12 reports) and anger (11 reports).

In 12 reports, time-to-onset was reported. Time-to-onset varied from 0 days to 4 months, with a median of 11 days. Fifteen reports mention that the drug was withdrawn, and the patient recovered (positive de-challenge), while only six reports that the drug withdrawn and there was no effect observed (negative de-challenge). None of the reports mention a positive re-challenge. In 42 reports, vortioxetine was the only suspect drug and no concomitant medication was reported. In 29 reports, vortioxetine was the only suspect drug but there was concomitant medication. In five reports there were drugs reported as "suspect": escitalopram (two reports), mirtazapine (one report), ondansetron (one report), and clonazepam/lamotrigine/lurasidone/venlafaxine (one report). Aggression is not a known side effect of ondansetron; however agitation is. One report also had clonazepam, lamotrigine, lurasidone and venlafaxine as suspect drugs. Aggression is a known ADR for escitalopram, mirtazapine, clonazepam, lamotrigine and venlafaxine, while agitation is a known ADR for ondansetron and lurasidone.

Illustrative case reports

Case 1

A 75-year-old female with severe depression was treated with vortioxetine after she experienced lack of effect with escitalopram. Within weeks of starting treatment, the patient was hospitalized due to aggressive behaviour, confused state, a cramp-like incident in her arms, a strange feeling of heavy arms, and a strange feeling in the body.

The patient had never before shown aggressive behaviour, but while on treatment with vortioxetine, severe aggression developed. The patient slammed wet dishcloths on the table, threw a box with shoes on the floor, banged on the walls and on the toilet door while her spouse was in the toilet. The patient was out of her mind, and the spouse described that the patient was completely out of balance, which he had never observed before.

Vortioxetine was discontinued 24 days after its initiation. Symptoms resolved while hospitalised.

Case 2

A 42-year-old male with acute depression, he had been treated previously with sertraline but discontinued it due to sexual side effects. The treatment with vortioxetine was initiated at 10 mg. The patient complained that he was irritable on the medication. The dose was increased to 15 mg, after which it was noted that he felt that he became more aggressive, which was not in his character. He described that he "almost came into conflict with people on a few occasions that could have led to an actual altercation". He himself stopped the medication. The patient considered other factors for the aggression (work, stress) but felt that vortioxetine was responsible for the change. At the time of this report, he had stopped the medication four days previously and was waiting to see if there was a difference.

Case 3

A 50-year-old female was treated for major depression with vortioxetine. The patient noted that after the start of the medication, she felt agitated, with motoric unrest. After increasing the dosage from 10 mg to 15 mg, the patient was aggressive and more agitated. The vortioxetine dose was subsequently decreased stepwise from 15 mg to 10 mg to 5 mg, and finally withdrawn. The patient recovered from the agitation/aggression within a week of the withdrawal. Concomitant medication was not reported. The patient had no known medical history, nor known past drug therapy.

Case 4

A 40-year-old male was started on vortioxetine for major depression. In the second week of therapy, the patient developed severe nausea and diarrhoea as well as a gradual onset of irritability and angry mood. During the third week the patient suffered from strong itching of the lower limbs at night in addition to continued nausea and diarrhoea and a headache every day starting in the morning. The patient reported his condition to his psychiatrist, but was told that these were usual adverse reactions. At the end of fourth week the patient experienced an attack of aggression which "resulted in the destruction of things". The patient visited the psychiatrist again, no hospitalization was needed, and his medication was immediately changed to Zoloft 100 mg.

Literature and Labelling

The EU product labelling intended for health care providers (the Summary of Product Characteristics in the EU) only warns that aggression has been observed in paediatric patients being treated with other antidepressants, without a specific mention of vortioxetine.[9] The labelling intended for patients (the Patient Information Leaflet) contains no mention of aggression or other similar terms.[10]

The US Package Insert (intended for both health care providers and patients) refers to the association of aggression with other antidepressants, but it also mentions an aggression-like term (sudden outbursts of anger) in specific association with discontinuation of vortioxetine.[11]

Discussion and Conclusion

Disproportionality analysis (IC analysis)[12] has revealed a statistically significant increased number of observed cases of aggression with vortioxetine compared to what is expected within the database. Exploration of VigiBase reveals a similarly significant increase in disproportionality for a number of related PT terms, including hostility, violence-related symptom, irritability, verbal abuse.

Review of the cases included in the drug-ADR combination has focused on the specific MedDRA PT "aggression" given the number of cases within the case series with sufficient and rich detail, enabling causality assessment. It is likely that additional clinically relevant cases could be identified by expansion of the case search using the High Level Term Behaviour and Socialisation Disturbances or the SMQ Hostility/Aggression.

Supporting evidence for possible causality from the case series are the wide geographic distribution of cases, a lack of evidence that aggression was part of a larger clinical syndrome in 26 cases, vortioxetine as the only reported drug in 42 reports (and the only suspected drug in 29 additional reports with concomitant medication), and the documentation of a positive de-challenge in 15 cases. A potential confounder in all cases is that of indication for treatment; however, aggression is not usually considered to be related to major depressive disorder which is the only indication for which vortioxetine is licensed. Cases 1 to 4 above were chosen to highlight a number of details which support the causality hypothesis: the clear onset of symptoms (noted to be out of character for these patients) after the initiation of therapy; the lack of apparent confounders, such as concomitant medications; dose-response relationship in two cases; and resolution of symptoms with discontinuation in three cases. Furthermore, three of the cases suggest a clinical pattern in which feelings of agitation/irritability precede the overt manifestation of aggression.

To explore the biological plausibility of a causal association between vortioxetine and aggression the relationship between serotonin and aggression has been reviewed. Serotonin is thought to have a role in the inhibition of impulses and the regulation of emotions and social functioning, which are domains linked to aggression.[13,14] Manchiaetal. recountthat 5-HTreceptors have been investigated in preclinical and clinical studies for their role in mental diseases but also specifically in aggressive behaviour. Involvement of 5-HT1A and 5-HT1B receptors in aggression has been confirmed by pharmacological studies indicating that 5-HT1A agonists and partial agonists and mixed 5-HT1A/5-HT1B partial agonists have potent anti-aggressive properties in animal paradigms of aggressive behaviour. Since vortioxetine is a 5-HT1B receptor partial agonist, anti-aggressive behaviour could possibly be expected. However, they stated that current knowledge does not yet clearly disentangle whether 5-HT dysfunction, most often a 5-HT deficiency, is the cause or the consequence of the aggressive/violent behaviour, of the underlying mental disease(s), or the expression of the comorbidity. Future studies are recommended to clarify the association between changes in 5-HT levels, altered activity of 5-HT receptors and their intracellular signalling cascades, and modifications of 5-HT genes, and in particular, the neurobiological link between the altered 5-HT machinery and aggressive behaviour in the context or in the absence of mental illness.[15]

A causal link between aggression and an analogous class of antidepressants, the SSRIs, has been explored in a number of published articles; however, there is a lack of consensus in the conclusions on causality. An article from Walsh and Dinan reviewed all published papers on Medline and other databases linking serotonin, SSRIs and aggression. They conclude that there is no convincing evidence to link SSRIs causally to violence and suicide. A small proportion of patients treated with SSRIs may become akathisic and others may show increases in anxiety in the initial phase of treatment, but no increased susceptibility to aggression nor suicidality can be connected with the SSRIs. In fact, SSRI treatment may reduce aggression, probably due to positive effects on the serotonergic dysfunction that is implicated in aggressive behaviour directed towards oneself or others.[16] In contrast, the review and analysis by Breggin states that evidence from many sources (clinical reports, controlled clinical trials and epidemiological studies) confirms that SSRIs commonly cause or exacerbate a wide range of abnormal mental and behavioural conditions. This can result in suicidality, violence and other forms of extreme abnormal behaviour. These include the production of feelings that often begin with lesser degrees of insomnia, nervousness, anxiety, hyperactivity and irritability and then progress toward more severe agitation, aggression, and varying degrees of mania. Another proposed mechanism is the production of a combined state of stimulation and depression (an agitated depression) with a high risk of suicide and violence. Additionally, SSRIs can be associated with the production of obsessive preoccupations and/or the production of akathisia, an inner agitation, both of which can lead to aggression against self or others.[17] In spite of the lack of consensus on causality, the Pharmacovigilance Risk Assessment Committee at the EMA concluded that the evidence was enough to include aggression in the product labelling for paroxetine in 2015.[18]

Review of regulatory documentation for vortioxetine has revealed that in pre-clinical studies performed to support the application for licensure, administration of the drug was associated with CNS-related clinical signs in mice, rats and dogs. These included salivation (rat and

dog), pupil dilatation (dog), and convulsions (dogs). Analysis of a subgroup of the clinical trial population ("the MDD short-term pool") revealed an increased proportion of the CNS events of dizziness, abnormal dreams and increased appetite in participants who received vortioxetine. However, the incidence of treatment-emergent adverse events within the SMQ Hostility/Aggression were found to be similar between the placebo group (2.8%) and the vortioxetine total group (1.9%).[2]

Pharmacokinetic data show that several CYP isoenzymes are involved in the metabolism of vortioxetine: CYP2D6, CYP2C9, CYP3A4/5, CYP2A6, CYP2C8, CYP2C19 and CYP2B6. CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carboxylic acid metabolite, and poor metabolizers (PM) of CYP2D6 have approximately twice the vortioxetine plasma concentration of extensive metabolizers (EM). According to the manufacturer, the approximately two- fold higher vortioxetine exposure in CYP2D6 PMs does not translate into significant changes in the safety and tolerability profile of vortioxetine relative to that in CYP2D6 EMs. However, the frequency of some adverse effects is doubled in the PM group versus the EM group, such as dizziness and pruritus.[2] A small study of 18 patients performed in the Netherlands found no evidence for a significant relationship between CYP2C19 and CYP2D6 polymorphisms and aggression in patients using SSRIs.[19] An expansion of this study using a larger cohort of patients to investigate the relationship between vortioxetine and aggression could be considered.

Given the complexity of the multi-modal actions of vortioxetine and the uncertainties surrounding the role of serotonin in aggression and the strength of the clinical support from the case series, there is adequate evidence to suggest a potential causal relationship between vortioxetine and aggression. The combination of pharmacokinetic data and the two cases suggesting the possibility of a dose response relationship could be used to hypothesize that patients who are CYP2D6 poor metabolizers are at an increased risk for aggression and other ADRs from vortioxetine. Current product information for vortioxetine does not sufficiently inform patients about the potential association with aggression, and the product labelling may need to be revised.

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