

Vortioxetine and aggression

Introduction

Vortioxetine (Brintellix®) is a structurally new type of psychotropic medication indicated for *the treatment of major depressive disorder in adults*[1]. It is considered to have a multimodal pharmacological mechanism of action. In vitro studies have revealed it to be a 5-HT₃, 5-HT₇, and 5-HT_{1D} receptor antagonist, a 5-HT_{1B} receptor partial agonist, a 5-HT_{1A} 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, 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 exerting additional effects such as increased synaptic plasticity and improved cognitive function[2]. Vortioxetine was granted market authorisation in the Netherlands in 2013[1].

Aggression is defined as “forceful physical, verbal, or symbolic action which may be appropriate and self-protective or inappropriate; aggression may be directed towards the environment, another person/personality, or towards the self”, as described 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[4].

The biological mechanism behind aggression is complex, involving several cortical and subcortical brain networks which are modulated by a 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-HT_{1A} and 5-HT_{2A} receptors, 5-HT transporters, DA D₁ and D₂ receptors, DA transporters, α₁- and α₂-adrenoceptors, the enzyme monoamine oxidase (MAO)-A, the GABA system (GABA_A and GABA_B receptors and GABA transaminase), the glutamate NMDA and AMPA receptors, and voltage-gated Na⁺ and Ca²⁺ channels[7;8]. Besides these biological factors, psychological and social factors can play a role in aggression.

Reports

From February 2015 until February 2019 the Netherlands Pharmacovigilance centre Lareb received six reports of aggression and/or agitation associated with the use of vortioxetine.

Table 1. Reports of vortioxetine associated with aggression and/or agitation in the Lareb database

| Patient, Sex, Age | Drug Indication for use | Concomitant medication | Suspected adverse drug reaction | Time to onset, Action with drug outcome |
|--|--|--|---|---|
| A, NL- LRB- 00255581, M, 11-20, Consumer | vortioxetine, 1 dd 10mg, anxiety disorder | colecalfiferol, finasteride | aggression, pruritus generalised, suicidal ideation | 5 weeks, drug withdrawn, recovered |
| B, NL- LRB- 189314, F, 51-60, Consumer | vortioxetine, 1 dd 10mg, depression | omeprazole, colecalfiferol, levothyroxine, quetiapine, lithium, diazepam, agomelatine | aggression, crying, dry skin, hostility, hot flush, paranoia, suicidal behaviour | 6 weeks, dose increased, recovering |
| C, NL- LRB- 205035, F, 41-50, Consumer | vortioxetine, 1 dd 10mg, depression | | aggression, agitation, nausea | 2 weeks, drug withdrawn, recovered |

| Patient, Sex, Age | Drug Indication for use | Concomitant medication | Suspected adverse drug reaction | Time to onset, Action with drug outcome |
|---|--|--|---|---|
| D, NL- LRB- 218753, F, 61-70, Pharmacist | vortioxetine, 1 dd 15mg, depression | omeprazole, nifedipine, atorvastatin, clobetasol, diclofenac, ibuprofen, oxazepam, zolpidem, venlafaxine, desloratadine, aluminiumacetate-tartrate | aggression | 4 months, drug withdrawn, recovering |
| E, NL- LRB- 205448, F, 41-50, Consumer | vortioxetine, 1 dd 10 mg, depression | | abnormal dreams, agitation, feeling hot, headache, influenza like illness, insomnia, pruritus, tension | 2 hours, dose not changed, recovered |
| F, NL- LRB- 207406, F, 41-50, Specialist doctor | vortioxetine, 1 dd 10mg, anxiety depression | escitalopram | agitation, muscle twitching, obsessive-compulsive disorder, tic | 6 days, drug withdrawn, recovered |

Additional information on the cases is given below:

Case C: aggression aggravated with increase of the dose from 10 mg to 15 mg. After withdrawal the patient recovered within a week.

Case E: the patient recovered from agitation after four days despite continued use of vortioxetine.

Other sources of information

SmPC

The SmPC of vortioxetine does not mention aggression as adverse drug reaction[1]. In 4.4 it says:

Use in paediatric population

Brintellix is not recommended for the treatment of depression in patients aged less than 18 years since the safety and efficacy of vortioxetine have not been established in this age group. In clinical studies in children and adolescents treated with **other antidepressants**, suicide-related behaviour (suicide attempt and suicidal thoughts) and **hostility (predominantly aggression, oppositional behaviour, anger)** were more frequently observed than in those treated with placebo.

Literature

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 [9;10]. Manchia et al [11] recount that 5-HT receptors 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 function of the 5-HT pathway and aggressive behaviour in the context or in the absence of mental illness.

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 with respect to conclusion on causality. An article from Walsh and Dinan[12] 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 akathic 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. In contrast, the review and analysis by Breggin[13] 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. In spite of the lack of consensus on causality, the EMA concluded that the evidence was enough to include aggression in the product labelling for paroxetine in 2015[14]. In 2018 the Uppsala Monitoring Centre (UMC) communicated in collaboration with Lareb a signal about vortioxetine and aggression in the UMC Signal document[15].

Databases

Table 2. Reports of aggression associated with the use of vortioxetine in the Lareb, WHO and Eudravigilance database[16;17]

| Database | Drug | ADR | Number of reports | ROR (95% CI) |
|----------------|--------------|------------|-------------------|-----------------|
| Lareb | vortioxetine | aggression | 4 | 12.8 [4.7-35.0] |
| WHO | vortioxetine | aggression | 88 | 3.9 [3.2-4.9] |
| Eudravigilance | vortioxetine | aggression | 47 | 4.8 [3.6-6.4] |

Prescription data[18].

| Drug | 2014 | 2015 | 2016 | 2017 |
|--------------|------|-------|-------|-------|
| vortioxetine | 30 | 1,966 | 3,221 | 3,623 |

Mechanism

SSRIs and vortioxetine increase serotonergic activity in the central nervous system by inhibition of neuronal reuptake of serotonin. Serotonin is supposed to have a role in the inhibition of impulses, the regulation of emotions and social functioning, which are domains linked to aggression[9]. Several mechanisms are postulated by which SSRIs might cause aggression. These include the production of feelings that often begins with lesser degrees of insomnia, nervousness, anxiety, hyperactivity and irritability and then progress towards 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. Furthermore, the production of obsessive preoccupations with aggression against self or others, often accompanied by a worsening of any pre-existing depression. Finally, the production of akathisia, an inner agitation, that causes heightened irritability and frustration with aggression against self or others[13]. However, underlying disease and environmental influences make it difficult to demonstrate an indisputable relation between aggression and the use of vortioxetine.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received six reports of aggression and/or agitation associated with the use of vortioxetine. These reports concerned five women and one man, with ages varying from 19 to 67 years. Aggression has been linked to serotonin in literature however, there is a lack of consensus in the conclusions on causality. Aggression is labelled in the SmPC of SSRIs such as paroxetine[14].

The association of vortioxetine and aggression is supported by a statistically significant disproportionality in the database of Lareb, WHO and Eudravigilance. This signal describes a possible association of vortioxetine and aggression.

Reference List

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- (17) Eudravigilance database. <http://bi.eudra.org> (access restricted) (Accessed on 12-3-2019)
- (18) GIPdatabase - Drug Information System of the Dutch Health Care Insurance Board. <http://www.gipatabank.nl> (Accessed on 12-3-2019)

This signal has been raised on April 10, 2019. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl