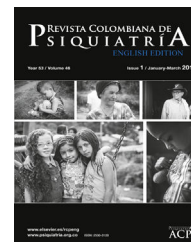




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Review Article

Activation syndrome in children and adolescents treated with selective serotonin reuptake inhibitors

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ABSTRACT

Introduction and objectives: Selective serotonin reuptake inhibitors (SSRIs) are medications used in child and adolescent psychiatry mainly for the treatment of depression, anxiety and obsessive compulsive disorder. In general, these medications are safe and well tolerated. However, they can cause adverse effects such as activation syndrome, which if not identified can negatively affect adherence and response to treatment. Activation syndrome has received little attention and can be difficult to recognise due to the lack of a clear definition and objective diagnostic measures, and also because it can be confused with a worsening of the psychiatric disorder or mania triggered by the antidepressants. For all the above, it is important that professionals who prescribe antidepressants in the paediatric population are able to identify and manage activation syndrome when it occurs. Our aim was to carry out a narrative review of activation syndrome in children and adolescents treated with SSRIs in terms of definition, prevalence, pathophysiology, associated factors, relationship with suicide risk, management strategies and recommendations for reducing the risk of suicidal behaviours when using antidepressants in this population.

Methods: We performed a non-systematic narrative review of activation syndrome in children and adolescents which involved finding information in PubMed, Ovid, EBSCO, ProQuest and Embase. Review articles, prospective and retrospective investigations, systematic reviews, meta-analyses and other articles related to activation syndrome in children and adolescents were selected. The search was limited to studies published in English and Spanish that involved children and adolescents and no limits were applied to the publication date or study design.

Results: A total of 62 articles were included, 61 of them in English. The results were grouped into the following topics: definition; prevalence; pathophysiology; associated factors; relationship with suicide risk; management strategies; and recommendations for reducing the risk of suicidal behaviours when using antidepressants in this population. Activation syndrome refers to a set of symptoms consisting of impulsiveness, restlessness, increased activity, insomnia, irritability, disinhibition and agitation. This syndrome is poorly characterised in terms of its definition, prevalence, risk factors and pathophysiology, a situation that limits its recognition and evaluation. There are many factors that predispose the development of the syndrome such as age, differences in brain development in the paediatric

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population, the characteristics of the patient or the antidepressant, disorders of neurological development, and the doses and plasma levels of the medications. It has been thought that activation syndrome may be related to suicidal tendencies. However, the evidence in support of this link is inconsistent and further studies are therefore necessary.

Conclusions: Activation syndrome with SSRI is a particularly important adverse effect in children and adolescents and, when it occurs, can cause lack of adherence to or discontinuation of treatment. Strict vigilance is therefore recommended during the use of these medications.

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Síndrome de activación en niños y adolescentes tratados con inhibidores selectivos de la recaptación de serotonina

R E S U M E N

Palabras clave:

Activación

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ISRS

Eventos adversos

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Introducción y objetivos: Los inhibidores selectivos de la recaptación de serotonina (ISRS) son medicamentos que se usan en psiquiatría de niños y adolescentes principalmente para el tratamiento de depresión, ansiedad y trastorno obsesivo compulsivo. En general, estos medicamentos son seguros y se toleran bien, pero pueden producir efectos adversos como el síndrome de activación, que si no se identifica puede afectar negativamente a la adherencia y la respuesta al tratamiento. El síndrome de activación ha recibido poca atención y existen dificultades en su reconocimiento por la falta de una definición clara y de medidas de diagnóstico objetivas y porque, además, puede confundirse con un empeoramiento del trastorno psiquiátrico de base o un viraje a manía con antidepresivos. Por todo lo anterior, es importante que los profesionales que prescriben antidepresivos a población pediátrica puedan identificar y tratar el síndrome de activación cuando se presente. El objetivo es desarrollar una revisión narrativa del síndrome de activación en niños y adolescentes tratados con ISRS en cuanto a su definición, prevalencia, fisiopatología, factores asociados y relación con el riesgo de suicidio, las estrategias de tratamiento y las recomendaciones para la reducción del riesgo de conductas suicidas al usar antidepresivos en esta población.

Métodos: Se realizó una revisión narrativa no sistemática del síndrome de activación en niños y adolescentes, la cual involucró la búsqueda de información en PubMed, Ovid, EBSCO, ProQuest y EMBASE. Se seleccionaron artículos de revisión, investigaciones prospectivas, retrospectivas, revisiones sistemáticas, metanálisis y demás artículos sobre el síndrome de activación en niños y adolescentes. La búsqueda se limitó a los estudios publicados en inglés y español que involucraran a niños y adolescentes y no se aplicaron límites en cuanto a la fecha de publicación o diseño del estudio.

Resultados: Se incluyeron un total de 62 artículos, 61 de ellos en inglés. Los resultados se agruparon en los siguientes temas: definición, prevalencia, fisiopatología, factores asociados, su relación con el riesgo de suicidio, estrategias de tratamiento y recomendaciones para la reducción del riesgo de conductas suicidas al usar antidepresivos en esta población. Se encontró que el síndrome de activación hace referencia a un conjunto de síntomas consistentes en impulsividad, inquietud, aumento de la actividad, insomnio, irritabilidad, desinhibición y agitación. Hasta el momento, este síndrome está mal caracterizado en cuanto a definición, prevalencia, factores de riesgo y fisiopatología, situación que limita su reconocimiento y evaluación. Existen factores que pueden predisponer a la aparición del síndrome, como la edad, las diferencias de desarrollo cerebral en la población pediátrica, las características del paciente o del antidepresivo, los trastornos del desarrollo neurológico y las dosis y concentraciones plasmáticas de los medicamentos. Se ha considerado que el síndrome de activación puede estar relacionado con tendencias suicidas; no obstante, la evidencia que respalda dicho vínculo es contradictoria, por lo cual son necesarios más estudios.

Conclusiones: El síndrome de activación con ISRS representa un efecto adverso particularmente importante en niños y adolescentes, y cuando se presenta puede causar la falta de adherencia o la suspensión del tratamiento, por lo cual se recomienda una vigilancia estricta durante el uso de estos medicamentos.

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Introduction

The first article on the selective serotonin reuptake inhibitor LY110140 (fluoxetine) was published in 1974. It was later shown that fluoxetine is a potent and selective inhibitor of the reuptake of this neurotransmitter, and has a relatively weak affinity for the norepinephrine transporter, which sets it pharmacologically apart from other antidepressants.^{1,2} The United States Food and Drug Administration (FDA) approved this drug in December 1987 and launched it on the market in January 1988 under the trade name Prozac®. Other SSRIs have since been developed, such as sertraline, citalopram, escitalopram, paroxetine and fluvoxamine.³

All SSRIs share the property of selective inhibition of serotonin reuptake, with consequent potentiation of the serotonergic postsynaptic effect, but as a group, they are structurally heterogeneous, and each one has unique pharmacological properties.⁴⁻⁷

Although originally approved for adults, they are currently widely prescribed to the paediatric population to treat various depressive, anxious and obsessive-compulsive symptoms. In general, SSRIs are medications well tolerated by children and adolescents. However, they can cause some adverse effects, such as gastrointestinal symptoms, headache, changes in appetite, sleep problems, alterations in sexual functioning and activation syndrome. Activation syndrome has received little attention, which is why it can be overlooked. This is due to the lack of a precise definition and the possibility of confusing it with a worsening of the underlying psychiatric disorder or mania triggered by the antidepressants. In these circumstances, activation syndrome is a serious adverse event. When it occurs, it can affect both adherence and response to treatment, and it is therefore important to consider when using SSRIs.

Definition

Activation syndrome represents a cluster of symptoms consisting of impulsiveness, restlessness, increased activity, insomnia, irritability, disinhibition and agitation.⁸⁻¹¹ To date, there is no standard definition, and it can vary according to the author. The syndrome is also poorly characterised in terms of prevalence, risk factors and pathophysiology. Some symptoms may not be caused by the drug but rather by the manifestations of the underlying psychiatric condition, which makes it difficult to recognise.^{12,13}

Prevalence of activation syndrome

Various studies have analysed activation syndrome either directly or indirectly. For example, in a prospective study by Riddle et al.¹⁴ (1990) with 24 children and adolescents aged 8–16 years treated with fluoxetine for obsessive-compulsive or depressive symptoms, it was found that 50% suffered behavioural side effects, such as motor restlessness (45%), sleep disturbance (45%), social disinhibition (25%) or a subjective feeling of excitement (12.5%). Discontinuation or dose

reduction resulted in complete resolution of these symptoms within 1–2 weeks.

In the 8-week double-blind, placebo-controlled study by Walkup et al.¹⁵ (2001), which included 128 children aged 6–17 years with social phobia, separation anxiety disorder or generalised anxiety disorder, increased motor activity was found in 27% of patients treated with fluvoxamine and in 12% of the placebo group. However, since the analysis was limited to motor activity, the occurrence of activation syndrome may have been underestimated.¹⁰

In a retrospective review of the medical records of 82 children with diagnoses of major depression or obsessive-compulsive disorder treated with SSRIs, Wilens et al.¹⁶ (2003) found that 22% suffered adverse events with treatment. Many were related to activation, such as irritability (15%), anxiety (10%), mania (6%), aggression (1%) and insomnia (17%). In this study, no statistically significant differences were observed with respect to the children's baseline diagnosis, and all psychiatric adverse events subsided after discontinuation of the medicinal product. Furthermore, 44% of patients with a previous event suffered a similar event when re-exposed to another SSRI.⁹

In another double-blind, placebo-controlled study, Reinblatt et al.¹² (2009) found that 10 of 22 children and adolescents with anxiety disorders treated with fluvoxamine experienced activation symptoms, compared to only one in the placebo group. It was found that a third of these symptoms occurred in the first month of treatment. Additionally, the mean blood fluvoxamine level at week eight was significantly higher in subjects who had adverse events compared to those who did not.¹⁰

A systematic review by Offidani et al.¹⁷ (2013), which evaluated the presence of mood elevation or behavioural activation in children under 18 years of age diagnosed with anxiety disorder or depression treated with antidepressants, found that activation rates during treatment were 13.8% in the first diagnosis, 11.2% in the second, and 3–10 times higher compared to placebo. The overall risk of activation regardless of diagnosis was 12.9% for antidepressant treatment and 3.69% for placebo.

A differential prevalence has also been found when comparing children and adolescents. For example, a study by Safer et al.¹⁸ (2006) which evaluated data on adverse events with SSRIs comparing double-blind and placebo-controlled studies by age groups, showed that activation syndrome occurred on average in 10.7% of children and 2.1% of adolescents. These results indicate a possible biological vulnerability to developing activation. Similarly, in a retrospective study by Zuckerman et al.¹⁹ (2007) in 39 children under 7 years of age treated with SSRIs, it was found that 21% of patients experienced behavioural activation, and this was the most common adverse event.⁹ In another study by Harris et al.²⁰ (2010) of 17 children and adolescents aged 7–17 years diagnosed with obsessive-compulsive disorder and treated with fluvoxamine, activation occurred in 17% and all were ≤12 years of age.⁹

Lastly, in the multimodal study of anxiety in children and adolescents by Rynn et al.²¹ (2015) 488 participants aged 7–17 years were randomised to cognitive behavioural therapy, sertraline, a combination of both or placebo, finding that the total number of psychiatric adverse events was significantly higher in children than in adolescents (31.7% compared to 23.1%),

especially disinhibition. This study highlights the importance of systematically monitoring adverse effects and using this information to guide medicinal product adjustment in the younger age group.⁹

Related factors

Among the factors involved in activation syndrome have been age, intellectual disability, Tourette's syndrome, panic disorder, developmental disorders such as autism, the individual characteristics of each drug and the doses used.^{10,18}

Age is a significant factor in the development of some adverse effects of antidepressants, due to the particular characteristics of the paediatric population in terms of its development, pharmacokinetics and pharmacodynamics. In these circumstances, when children are treated with antidepressants, they suffer more total and activation-related adverse events compared to adolescents and, because of these problems, they are more likely to discontinue treatment.⁹

Some distinctive features to consider in children are a smaller body than adults, a larger liver and kidney tissue mass adjusted for body weight, higher water content, and less fat and plasma albumin to which the drug can bind. Consequently, the volume of distribution of a drug tends to be greater in children than in adults. Additionally, children have greater drug extraction during the first pass through the liver, have lower bioavailability, and metabolism and elimination are faster. Furthermore, neurotransmitter receptors change during development, peaking in the preschool years and progressively declining until late adolescence, when adult levels are reached.²²

Another related factor corresponds to neurological development disorders, which increase the risk of activation syndrome. For example, a study by Carlson et al.,²³ (2003) which examined the presence of drug-induced behavioural disinhibition in 267 hospitalised children found this occurred in 7.5% of patients, and that the factors that increased the risk were attention deficit and hyperactivity disorder, pervasive developmental disorder and selective use of SSRIs.

In a retrospective analysis by García et al.,²⁴ (2018) in a group of 139 children and adolescents hospitalised and treated with SSRIs, activation was observed in 20.9% of the patients, and among the factors statistically significantly related to its appearance were age ≤ 12 years old and a comorbid diagnosis of autism spectrum disorder.

It has been reported that although activation can occur at any time during treatment with antidepressants, it seems to occur more frequently during the first 2–3 weeks after starting the drug. Furthermore, most studies indicate higher doses are associated with higher activation rates, and the syndrome resolves when the antidepressant is reduced or discontinued.^{9,10}

Last of all, variations in pharmacokinetics (for example, slow hepatic biotransformation) or pharmacodynamics (for example, serotonin transporter polymorphisms) have been found to cause individual reactions to antidepressants and may create vulnerability to certain adverse effects.¹⁰ Fluoxetine and paroxetine are largely metabolised by cytochrome P450 isoenzyme 2D6 and are also potent inhibitors of the

same. Therefore, the reduced clearance of these drugs in poor metabolisers of the enzyme may lead to higher plasma concentrations, generating a greater risk of activation syndrome.^{25,26}

Pathophysiology of activation syndrome

Due to the complexity of evaluating and defining activation, it has been difficult to clearly explain its pathophysiology. However, one of the mechanisms which has been proposed is the change in serotonin concentrations that occurs after starting the antidepressant.⁹ SSRIs prevent serotonin reuptake by blocking its transporters. This increases the availability of the neurotransmitter to stimulate the postsynaptic neuron, and through additional mechanisms, to bring about the antidepressant effect.²⁷

Despite that, there is a delay of 2–4 weeks until the clinical onset of antidepressant effects, and it is observed that in this period, the excess of serotonin activates the 5-HT_{1A} autoreceptors in the presynaptic neuron to prevent its additional release. Therefore, the acute adverse effects of SSRIs could be the result of the decrease in serotonin mediated by the receptors mentioned above during the initial phase of treatment. Furthermore, the desensitisation of these autoreceptors and the recovery of normal serotonergic neuronal activation occurs after 2–4 weeks of exposure to SSRIs, which correlates with the appearance of the response to these drugs.^{27,28}

The rate at which SSRIs stimulate 5-HT_{1A} receptors is proportional to the peak concentration of the drug after administration, so we would expect the negative behavioural effects of SSRI treatment to be proportional to the rate of increase in its concentration in the brain.²⁷ Furthermore, some clinical studies report that hyposerotonergic states (low cerebrospinal fluid levels of 5-hydroxyindoleacetic acid, a metabolite of serotonin) correlate with increased impulsive and violent behaviour, which could also be related to activation.^{29,30}

The initial decrease in serotonergic release under the mechanisms described could compromise patients' ability to self-regulate their behaviour and generate disinhibition related to activation, which in turn can lead to impulse control problems and self-aggressive and hetero-aggressive behaviour.¹⁰

Other theories have pointed out that SSRIs are associated with functional changes in circuits that include the prefrontal cortex and the amygdala. However, the degree to which a particular antidepressant might enhance or dampen activity in this circuit is not fully understood.⁹

Another theory suggests activation symptoms with antidepressants represent a variant of the manic phase of bipolar affective disorder (BAD) in depressed children and adolescents who have not yet experienced a spontaneous episode of mania or hypomania.¹⁶ Although it is unclear whether SSRIs can accelerate or cause the development of mania, it is important to use caution in children and adolescents at high risk for BAD; for example, those with early-onset depression, recurrent clinical course, subthreshold hypomanic and/or mixed symptoms, atypical depression, psychotic symptoms, adverse

response to antidepressants, and family history of BAD and/or completed suicide.³¹⁻³⁴

Studies have been conducted in an attempt to clarify the importance of activation, hypomania and mania associated with the use of antidepressants in children and adolescents. Faedda et al.³⁵ (2004) retrospectively analysed 82 patients with a diagnosis of paediatric BAD. They found that 69% were administered an antidepressant or stimulant at least once and that 58% of those exposed to these medications met criteria for emerging mania, with an average latency of 14 days. A much higher risk was also observed with antidepressants than with stimulants.

In a prospective study by Strawn et al.,³⁶ (2014) which evaluated the safety and tolerability of SSRIs in children and adolescents with depressive or anxiety disorders and a family history of BAD, adverse events occurred in 57% of the study group. Many of them were related to activation; for example, irritability, aggression, impulsiveness or hyperactivity. In general, younger patients were more likely to experience more antidepressant-induced adverse events and discontinue treatment compared to older patients.^{9,10,36}

In another study by Martin et al.,³⁷ (2004) evidence of mania and hypomania was found in 5.4% of more than 87,000 young patients aged 5-29 years during the use of antidepressants, showing a conversion rate three times higher among those exposed to these medications and a higher risk in the 10-14-year-old age group.³⁸ In a systematic review by Offidani et al.¹⁷ (2013) on the use of these medicinal products in juvenile depression and anxiety, it was also found that the overall rates of mania or hypomania were 8.19% with antidepressant treatment and 0.17% without it.

Lastly, it is important to remember that paediatric BAD has particular diagnostic challenges due to the influence of development on symptoms and the course of the disease, the frequent symptom overlap, and comorbidity with other conditions, such as attention deficit and hyperactivity disorder, depression, anxiety and behavioural problems, the symptoms of which can also be confused with activation syndrome.³⁵

Activation induced by antidepressants and its relationship with suicide risk

There are differences in opinion about the possible increase in suicidal ideation and behaviour with the use of antidepressants. However, the mechanism by which this happens is unclear. Some researchers speculate that activation syndrome may be related to such suicidal behaviours, but the evidence is contradictory, and methods and scales to objectively measure these events are limited.^{9,10,39}

In 2004, the FDA issued a warning indicating that antidepressants were associated with an increased risk of suicidal thoughts and behaviours in children and adolescents. It noted that after initiation of therapy, patients should be closely monitored for clinical worsening, suicidal tendencies, or unusual behaviour changes. The risk of suicide with these drugs was identified in a pooled analysis of 24 short-term placebo-controlled trials using nine antidepressant drugs in children and adolescents with major depressive disorder, obsessive-compulsive disorder and other psychiatric disorders. The

analysis showed a higher risk of suicide during the first months of treatment in those who received antidepressants. It also demonstrated that with the use of the drug, the average risk of such events was 4%, which represents twice the risk than with placebo (2%). However, no completed suicides occurred in these trials.⁴⁰⁻⁴⁴ In response to the above, there was a decrease in antidepressant prescribing rates due to the questions raised by the study and the need to carefully ponder the benefits and risks of their use in each patient.^{10,45-47}

Other studies indicate that antidepressant-induced behavioural activation is not a trigger for suicidal behaviour. For example, analysis of the Treatment for Adolescents with Depression Study (TADS) database⁴⁸ did not show an association between activation symptoms and suicidal behaviour. This was a 36-week randomised controlled clinical trial in 439 children and adolescents with major depression on drug and psychotherapeutic treatment. It was conducted to determine whether suicidal events occurring early in treatment were predictable by characteristics such as the severity of depression or were preceded by clinical deterioration or symptoms such as irritability, akathisia, sleep interruption or mania. Of the sample studied, 10% had at least one suicidal event, but only one patient experienced behavioural activation symptoms such as insomnia, emotional lability and irritability in the two weeks prior to a suicidal event. The authors reported that most suicidal events occurred in the context of persistent depression, insufficient improvement and acute interpersonal conflict. Furthermore, there was no evidence that drug-induced behavioural activation was a precursor, and the severity of self-rated suicidal ideation and depressive symptoms was found to predict the onset of suicidal tendencies during treatment.⁴⁸

In addition to all the above, activation syndrome has to be distinguished from energising phenomena that occur when a depressed patient has suicidal thoughts, even though they lack the energy to commit suicide. In such circumstances, in the early phase of antidepressant treatment, the patient's energy increases, but the mood has not yet improved, which creates a greater risk of the patient committing suicide. The antidepressant does not therefore actually cause suicide, but rather restores the lack of energy.^{10,11}

It is, therefore, necessary to consider that activation syndrome is not the only factor related to suicidal behaviour in patients treated with antidepressants. Other elements that increase the likelihood of events of this type are: susceptibility to suffering from BAD; the presence of non-suicidal self-harm and high degree of baseline suicidal ideation; lack of response to treatment with progression of the initial disorder; family conflicts; drug abuse; and developmental differences.^{11,49,50} In this last point, it has been found that a lack of maturity in pre-frontal myelination could predispose to impulsiveness, and higher densities of 5HT1A and 5HT2A serotonergic receptors have been found in younger individuals. This suggests that a higher density of 5HT1A receptors could lead to lower serotonergic production and be associated with suicide attempts with greater lethality and lack of response to SSRIs. In turn, a higher density of 5HT2A receptors has been associated with impulsive aggression, a key risk factor for juvenile suicide.⁴⁹

Treatment of antidepressant-related activation syndrome

Strategies for the prevention of activation syndrome and other side effects include starting antidepressants at low doses and gradually increasing them to therapeutic doses.⁹

If a patient develops activation syndrome, there is evidence that lowering the dose or discontinuing the drug may be effective in reducing this side effect.

Another strategy is to switch to another antidepressant. Still, it should be considered that patients who have experienced activation with one agent are more likely to suffer this side effect again with another drug.

Medication compliance should also be evaluated, given that abrupt discontinuation of the medication can cause a discontinuation syndrome that resembles activation symptoms.^{9,51,52}

Strategies to minimise the risk of suicidal behaviour when using antidepressants in children and adolescents

Education: patients and caregivers should be instructed about the potential adverse effects of antidepressants, such as mania, agitation, akathisia and sleep pattern disturbances, which could increase the risk of suicidal events. It should also be explained that there is a small risk of suicidal events in clinical trials, but that the number of children and adolescents who benefit from treatment is much greater than the number of patients who suffer these events.^{49,53–55} It is important to emphasise that depressive symptoms will not resolve immediately after starting to take an antidepressant, and that the likelihood of obtaining symptomatic relief with the medication is greater compared to the risk of engaging in suicidal behaviour.^{52,56}

Close monitoring during treatment initiation and dose changes: suicidal events tend to occur early in treatment.⁵⁷ Patients should be seen weekly for the first four weeks after starting the drug. If this is not possible, they should be followed up by telephone or other technologies. It is also important to control adherence to treatment, since lack of adherence is associated with poor response.^{49,55,58}

Seriously consider stopping the antidepressant or lowering the dose in the case of adverse effects: the onset of mania, agitation, akathisia, worsening depression, severe anxiety or suicidal ideation associated with starting the medicinal product or changing the dose should be taken seriously. If there are no other reasons to explain these adverse events, the dose should be reduced or the antidepressant discontinued.⁴⁹

Rational dosage: start the medication gradually, and increase the dose according to response and tolerance.⁴⁹

Seek a rapid response with the treatment: there is some evidence that the combination of medications and cognitive behavioural therapy generates a faster and more effective response in reducing depressive and anxious symptoms.^{49,59,60}

Identify the biopsychosocial factors and comorbidities that generate the risk of suicidal events and resistance to treatment.^{49,61,62}

Conclusions

Activation symptoms with SSRIs are a significant adverse event in children and adolescents which, when they occur, increase the likelihood of discontinuing the drug and affecting therapeutic response.

Determining the syndrome is complicated, because there is currently no precise definition, and there are no objective measures to evaluate it. It is also difficult to distinguish it from a worsening of the underlying psychiatric disorder or mania triggered by the antidepressants.

Some factors may predispose to the development of the syndrome, such as age, differences in brain development in the paediatric population, particular characteristics of the patient or the drug, neurological development disorders, doses and plasma concentrations of the medications. It has been considered that this syndrome may be related to suicidal tendencies, although the evidence to support this connection is contradictory, which is why more studies are necessary.

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Conflicts of interest

None.

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