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Association Between Antidepressant Use and the Risk of Suicide in Children and Adolescents

M. Raissouni[1*], S. Benhammou[1], H. Kisra[1]

[1]Faculty of Medicine and Pharmacy, Arrazi University Psychiatric Hospital, Salé, Mohammed V University, Rabat, Morocco

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***Corresponding author:** M. Raissouni
Faculty of Medicine and Pharmacy, Arrazi University Psychiatric Hospital, Salé, Mohammed V University, Rabat, Morocco

Abstract **Original Research Article**

In recent years, the prescription of antidepressants for children has come under serious scrutiny, as some studies have shown an increased risk of suicide among those treated in this way. The main aim of this study is to investigate the causal relationship between antidepressant use and suicidal behaviour in children and adolescents. We reviewed the literature on the Google Scholar, pubmed, science direct database. The data in the literature were contradictory; while it has now been demonstrated that SSRIs very moderately increase the risk of suicide ideation and attempts, with venlafaxine, paroxetine and sertraline in particular showing a higher risk than other SSRIs such as fluoxetine and citalopram, several studies show that their use is associated with a significant reduction in suicide rates in children and adolescents. There is currently no certainty of a causal relationship between antidepressants and suicidality in children and adolescents, so the mechanisms are still poorly understood.

Keywords: child, adolescents, suicide, risk, antidepressants, prescription, SSRI.

INTRODUCTION

Antidepressants are often prescribed to treat major depression in adults, but they are also increasingly being used in children and adolescents. However, there are concerns regarding their safety and efficacy in this population, especially due to the significant increase in the risk of suicide associated with the use of antidepressants in children and adolescents [1, 2].

In this article, we will examine the current research on this topic and discuss the current status of practical guidelines and recommendations for prescribing antidepressants to children and adolescents.

METHODS

We reviewed the literature based on Google Scholar, pubmed, direct science using the keywords antidepressants, suicide, side effects, children, adolescents.

RESULTS

Indications for antidepressants in children and adolescents:

- **Depression:** Antidepressants are recommended for children and adolescents with moderate to severe depression when there has been an inadequate response to psychotherapy [3]. Although it is recommended that antidepressant treatment be accompanied by concomitant psychotherapy, provision is also made for antidepressant monotherapy [3]. Tricyclic antidepressants (ATC), the pillars of treatment in the past, have not proven to be an effective pharmacological treatment for depression in youth [4, 5].
- **Obsessive Compulsive Disorder (OCD):** Several studies have demonstrated the efficacy of SSRIs (fluoxetine, sertraline, fluvoxamine, paroxetine) in OCD in children and adolescents [6, 7]. Of the tricyclic antidepressants, only clomipramine has been shown to be effective in OCD in children and adolescents [6, 8] and in this indication is superior to SSRIs [9].
- **Anxiety Disorders:** Several studies have demonstrated the efficacy of SSRIs (fluoxetine, sertraline, fluvoxamine, paroxetine) and venlafaxine in anxiety disorders of children and adolescents (separation anxiety, social phobia, generalized anxiety) [6, 8, 10]. No tricyclic antidepressants have been shown to be effective in anxiety disorders in children and adolescents [1, 2].

Side Effects of Antidepressants

Since SSRIs are the main antidepressant treatments prescribed in young people (other antidepressants are rarely used in young people), only the side effects of SSRIs are monoamine oxidase inhibitors (MAOI) [11]. will be discussed here. In the case of tricyclics, anticholinergic side effects and cardiac toxicity are the main side effects, while hypertensive seizures are the main risk of.

Suicidality

It has been suggested that SSRIs may, paradoxically, induce suicidal behaviour in youth. Verifying the veracity of this proposal is not easy because depression itself increases the risk of suicide [11].

SSRIs can induce akathisia, agitation, irritability and disinhibition. Like other antidepressants, SSRIs can also induce a manic turn.

Other Side Effects [11]

SSRIs are also associated with high rates of agitation, akathisia, nightmares and sleep disorders, gastrointestinal problems, weight gain, sexual dysfunction (decreased libido, difficulty ejaculating, or impotence) and increased risk of bleeding. Most of these side effects are dose-dependent and can be controlled by dose reduction. More recently, it has been shown that SSRI treatments slightly increase the rate of birth defects, especially heart defects. Thus, they should be avoided during the first months of pregnancy.

Antidepressants and Suicidal Effects in Children and Adolescents

Concerns about the increased risk of suicide, attempted suicide and suicidal ideation (collectively referred to as suicidal behaviour) among people receiving SSRIs were first raised in 2003 [12]. Meta-analyses examining the risk of suicide-related behaviour showed a consistent and modest increased risk for people taking SSRIs compared to placebo [13, 14]. Evidence of these risks has led to the action of regulatory bodies: the Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency (CSM/MHRA) in the UK [15, 16], the European Medicines Agency [17], and the U.S. Food and Drug Administration [18] have all warned practitioners about the use of SSRIs in children and adolescents, including a black box warning label of the FDA published on September 14, 2004, which advises health care providers of this evidence of an increased risk of suicidal behaviour [18].

- **The Causal Link is Contradictory:**

On the one hand, pharmaco-epidemiological and ecological studies suggest that increased use of SSRIs may have led not to an increase but rather to a decrease in youth suicides [11]. On the other hand, a meta-analysis carried out by the FDA of controlled trials with more than 4400 children and adolescents shows a significant increase even if small (2%) of the incidence of short-term suicidality (suicidal thoughts, suicide attempts) in youth receiving antidepressants, most often these were SSRIs compared to placebo [11]. There was no successful suicide. This has led to warnings from the FDA and regulators in other countries about this risk [11].

At the same time, new generation antidepressants have been increasingly used over the past 20 years [19, 20], early studies suggesting that they were well tolerated [21]. Efficacy reviews have shown modest effects of these antidepressants over the past two decades for example, [22-24] and also raised concerns about the increased risk of suicide attempts and suicidal ideation (collectively referred to as suicide-related behaviour) [13, 14, 22, 23].

In the same context, the impact of these actions by regulators and reactions to them in the media are unclear, with some early evidence of reduced prescriptions [25, 26] and more recent evidence suggesting a continued increase in the prescription of antidepressants [27, 28].

Some Studies Include:

Bridge JA *et al.*, [29]: For all antidepressants, primarily SSRIs, a meta-analysis including 15 randomized controlled trials on depression reported the number of youth needed to be treated for a positive outcome (NNT), ranging from 4 (for fluoxetine) to 20 (for nematode), with an average of 10 for all treatments (Bridge *et al.*, 2007). In other words, 4 depressed youth should be treated with fluoxetine for a youth to improve as a result of treatment (as opposed to other factors such as the placebo effect or the natural course of the disease). The same meta-analysis reported the number of youth to be treated for harm (NNH) - defined as the onset of suicidal behaviour - ranging from 112 (from 13 depression trials) to 200 (from 6 OCD trials) and 143 (of 6 anxiety disorders trials excluding OCD), with a common average of 143. For example, 112 depressed teenagers would need to be treated with antidepressants in order for 1 to develop suicidal behaviour attributable to treatment. In short, for all indications, the benefits of antidepressants appear to far outweigh the risks of suicidal ideation/suicide attempt.

Whittington *et al.*, [30]: The results presented in Table I show that the risk of serious adverse effects, including ideas and attempts at suicide, with an SSRI rather than a placebo is higher in unpublished studies than in published studies. This risk is also lower for fluoxetine than for other SSRIs, including sertraline and paroxetine.

Wong *et al.*, [31]: Data show that the incidence of "possible suicide-related events" and suicide attempts is higher among children and adolescents with major depressive disorder treated with SSRI (Tables II and III) than those treated with placebo.

TABLEAU I

Fréquence des effets indésirables observés avec les ISRS dans le trouble dépressif majeur chez l'enfant et l'adolescent. Analyse des étud contrôlées contre placebo publiées et non publiées

Effets indésirables (EI)	Étude	ISRS (%)	Placebo (%)	Risque relatif (IC 95 %)
Fluoxétine				
EI sérieux	Emslie 2002 [18]	0,9	3,6	0,25 (0,03-2,22)
Comportement suicidaire	NP	3,6	3,8	0,94 (0,37-2,40)
Tentative de suicide	NP	2,4	1,9	1,26 (0,36-4,40)
Arrêt du traitement en raison des EI	Emslie 1997 [19]	8,3	2	
	Emslie 2002 [18]	4,5	8,1	1,19 (0,18-7,85)
Sertraline				
EI sérieux	Wagner 2003 [16]	3,7	3,2	1,14 (0,39-3,32)
Idées ou tentative de suicide	Wagner 2003 [16]	2,6	1	2,43 (0,48-12,39)
Arrêt du traitement en raison des EI	Wagner 2003 [16]	8,9	2,6	3,36 (1,27-8,93)
Paroxétine				
EI sérieux	Keller 2001 [10]	11,8	2,2	5,15 (1,17-22,56)
	NP	12	6,4	1,87 (0,79-4,46)
Idées ou tentative de suicide	Keller 2001 [10]	5,3	0	10,30 (0,58-183,53)
Arrêt du traitement en raison des EI	Keller 2001 [10]	9,6	6,8	1,40 (0,52-3,78)
Citalopram				
EI	NP1	84,2	69,4	1,13 (1,01-1,27)
	NP2	75,2	70,5	
Tentative de suicide	NP1	1,1	2,3	1,99 (0,83-4,77)
	NP2	11,5	4,4	
Arrêt du traitement en raison des EI	NP1	5,6	5,8	1,20 (0,62-2,35)
	NP2	10,7	8	

NP : étude non publiée ; IC : intervalle de confiance.
Source : Whittington *et al.* Selective serotonin reuptake inhibitors in childhood depression: systematic review of published *versus* unpublished data. Lancet. 2004; 363: 1341-5.

TABLEAU II

Fréquence des "événements possiblement apparentés au suicide" avec les ISRS, trouvée dans les études contrôlées contre placebo dans le trouble dépressif majeur chez l'enfant et l'adolescent

Étude	ISRS (%)	Placebo (%)
Fluoxétine		
1	0	5,3
2	3,7	3,6
3	4,2	4,2
Sertraline		
1	4,1	0
2	2,2	2,2
Paroxétine		
1	6,5	1,1
2	3,9	4,2
3	1	1
Citalopram		
1	1	2
2	13	8

Source : rapport de la *Food and Drug Administration*, cité par Wong *et al.* Use of selective serotonin reuptake inhibitors in children and adolescents. Drug Saf. 2004; 27: 991-1000.

TABLEAU III

Fréquence des tentatives de suicide lors d'un traitement par ISRS trouvée dans les études contrôlées contre placebo dans le trouble dépressif majeur chez l'enfant et l'adolescent

Étude	ISRS (%)	Placebo (%)
Fluoxétine		
1	0	5,3
2	0,9	1,8
3	4,2	0
Sertraline		
1	1	0
2	2,2	2,2
Paroxétine		
1	5,4	0
2	3,9	4,2
3	1	1
Citalopram		
1	1	1
2	13	8

Source : rapport de la *Food and Drug Administration*, cité par Wong *et al.* Use of selective serotonin reuptake inhibitors in children and adolescents. Drug Saf. 2004; 27: 991-1000.

In contrast, Wong *et al.*, [31] point out that there has been a decrease in youth suicide rates (age 15-24) for about 14 years, coinciding with the significant increase in antidepressant prescriptions, particularly SSRIs, among adolescents.

Three studies, conducted in Finland, the United States and Sweden, confirm this relationship between the decrease in suicide rates and the increase in

SSRI prescriptions, especially among adolescents [32-34].

The study by Olfson *et al.,* [33] shows that a 1% increase in the use of antidepressants in adolescents is associated with a decrease of 0.23 suicide/100,000 adolescents per year.

- **Causal Link Assumptions:**

The mechanisms explaining the relationship between antidepressants and suicidal events in young subjects are not known with certainty. Several assumptions were made:

SSRIs, such as paroxetine, are primarily metabolized through cytochrome P450 2D6. Their clearance is higher in children and adolescents aged 6 to 17 than in adults aged 20 to 30. For some authors, these pharmacokinetic features would affect the efficacy and tolerance of SSRIs in children and adolescents [35].

Leeder [36] notes that it is difficult to know whether the suicidal symptoms are the consequence of the pharmacological peculiarities observed in children and adolescents because of the maturation processes, or if they represent only a developmental variation in the clinical expression of depression.

Limit:

Most studies have focused on the use of antidepressants in depression but not in other disorders such as OCD and anxiety disorders.

CONCLUSION

Based on this data, it is necessary for patients to be informed of this risk and for clinicians to put in place surveillance strategies, such as weekly reassessment of the suicidal risk during the first month of treatment, and offer therapeutic education to the patient and family to detect behavioural changes (such as agitation) when treatment is first initiated [11].

Thus, the use of antidepressants in children and adolescents should only be considered as a last resort and should be supervised by a qualified health professional [11].

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