SSRIs, Suicide and Violent Behavior: Is there a Need for a Better Definition of the Depressive State?

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Abstract: To what extent do SSRIs increase the risk of suicide or violent behavior? Recent data indicate that some SSRIs lack a favorable 'risk–benefit' profile for treating childhood and adolescent depression. In addition, certain recent documents have cast doubt on previous conclusions dissociating antidepressant from violence.

Beyond the debate on the need for improved transparency in clinical studies, this controversy raises other critical issues of SSRI use that merit our consideration.

Firstly, is there an overuse of antidepressants, and does the risk of suicide increase with the prescription of antidepressants in the whole population? Secondly, is the response to antidepressants modified during adolescence? If so, by what mechanisms? We know that SSRI treatment can trigger mood changes in undiagnosed young bipolar patients resulting in agitation and disinhibition, and such effects may lead to suicide and violence.

Thirdly, recent extensive literature has shown that some cases of depression are worsened by antidepressants and new data has suggested that bipolar depression can be improved by atypical antipsychotics. Finally, current criteria defining the depressive state are very similar to those employed during the 19^{th} century, a pre-therapeutic period. Currently, while it is recognised that depressive mood is a very broad construct, there is still only one definition in international classifications to describe a major depressive episode. There is a clear need to develop an evidence-based approach to psychiatry aiming at delineating diagnostic categories predictive of the response to treatments.

Keywords: Emotional reactivity, phenotype, depression, SSRI.

INTRODUCTION

Recent reports and studies have triggered a debate concerning the safety of selective serotonin reuptake inhibitors (SSRIs) in the treatment of childhood depression [1]. These drugs are suspected of being associated with an increased risk of suicide behavior.

The UK Committee on Safety of Medicines (CSM) undertook a review of the efficacy and safety of SSRIs in pediatric major depressive disorder. In view of the CMS report, the Medicines and Healthcare products Regulatory Agency (MHRA) released a statement contraindicating the use of all SSRIs other than fluoxetine as new treatment for patients younger than 18 years of age with depressive illness. The US Food and Drug Administration has also issued a warning about the increased risk of suicidality in young people being treated with antidepressant.

The controversy grew with the suspicion of lack of transparency in clinical studies. Whittington and colleagues [2] investigated in a meta-analysis the risk-benefit profile of individual SSRIs in childhood using published and unpublished data. They performed a meta-analysis of data from randomized controlled trials that evaluated SSRI versus placebo in participants aged 5-18 years. They assessed the following outcomes: remission, response to treatment, depressive symptom scores, serious adverse events, suicide-related behavior and discontinuation of treatment because of adverse events. The conclusion of this study was that published data suggests a favorable risk-benefit profile for SSRIs. However, addition of unpublished data indicates that risks could outweigh benefits of these drugs (except fluoxetine) for treating depression in children and young people.

Concerning the question that SSRIs might increase suicidal ideation in this population, it was not possible to clearly conclude. Indeed, the studies included in the analysis were not designed to investigate events such as suicide, and therefore are unlikely to have sufficient statistical power to detect potential risk. However, for some SSRIs the combination of published and unpublished data was not able to show a clear benefit for the use of these drugs in this group of patients.

In response to this debate, in September 2004, a Food and Drug Administration joint advisory committee voted to recommend that a "black-box" warning label be required for antidepressant drugs, indicating that they increase the risk of suicidal thinking and behavior "suicidality" in pediatric patients [3]. Finally, it seems that SSRIs should not be considered for use as first-line treatment in mild or moderate depression in childhood, where psychological interventions are the mainstay [1]. This statement is also strengthened by the high proportion of placebo response in this population.

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Beyond the polemics about transparency, this leads to some fundamental questions. Since the introduction of newer safer antidepressant treatment during the last decade, there may have been an increased use in the treatment of depression. Is there a possible over use? Or is there an inadequate use of antidepressants? Depressive mood is a very broad construct and includes many clinical subtypes, however there is only one definition in current classifications to describe a major depressive episode. If there are different responses to antidepressants in the broad spectrum of depressive mood, there is a need to define subtypes of depression as a function of the response to treatment. The polemics triggered by the treatment of adolescent depression induces more general issues about the concept of depression. The aim of this review is to further discuss these fundamental issues.

Is there a Possible Over Use of Antidepressant?

Many factors may impact on the risk of suicide such as social, cultural, psychological or biological factors, but 90 % of suicides are associated with psychiatric illness and more specifically mood disorders [4].

In the general population, it seems that an increase in the prescription of antidepressants correlates with a decrease in suicide rate, as shown by analyzing national population data sets. In Sweden, doubling prescriptions for SSRIs correlated with a 25% decrease in the suicide rate [5] and this tendency was also found in others countries such as Italy [6], Australia [7] and the US [8]. However, suicide rates have raised in Japan in the last 4 years, as indeed did the use of SSRIs [9] and there is no evidence for a benefit of the increase in antidepressant treatment in Iceland concerning suicide rate [10]. More recently, Gibbons and colleagues [11] have examined the association between antidepressant prescription and suicide rate by analyzing their association at the county level across the United States. They have shown that SSRIs and other new-generation non-SSRIs are associated with lower suicide rates over time. In contrast, a positive association between tricyclic antidepressant prescription and suicide rate was observed. The authors concluded that these results may reflect SSRI and other new-generation non-SSRI efficacy, and treatment compliance, as well as low toxicity in the event of a suicide attempt by overdose, and a better quality of mental health care.

There is no clear evidence that the increase in the prescription of antidepressants is always correlated with a decrease in suicide rate. It even seems that tricyclic agents could increase the risk of suicide. Moreover, it may be difficult to dissociate the impact of the global improvement of mental health from the consequences of the antidepressant prescription by itself. However, the impact of antidepressants seems better in the general population than in adolescents.

What can Explain this Apparent Discrepancy in the Antidepressant Efficacy Between the General Population and Children and Adolescents?

A possible explanation for this discrepancy might be that a substantial proportion of depressed children and adolescents may belong to the bipolar disorder spectrum [12]. Many arguments are in favor of this possibility. Bipolar disorders associating manic or hypomanic and depressive episodes are clearly under diagnosed, and there is a mean 8-year delay between the onset of the illness and the correct diagnosis. In the absence of psychotic features during episodes, the most common previous diagnosis was unipolar (recurrent) major depressive disorder [13]. The onset of bipolar disorder is earlier than that of unipolar major depressive disorder [14] and it seems clearly that bipolar depression is far more common than previously appreciated [15]. However, because depressive symptoms were present during a higher proportion of the time in comparison to hypomanic and manic symptoms, the misdiagnosis is frequent [16].

Unfortunately, bipolar disorders with early onset are associated with greater severity and poorer long-term outcome [17]. This early form of the illness is associated with higher rates of suicide attempts and completion, substance abuse, disturbed interpersonal relationships, and multiple hospitalizations. In addition, the natural course of early onset bipolar disorders tends to be chronic and continuous, rather than episodic and acute, with more rapid-cycling and mixed manic states [18]. Moreover, young patients experience severe irritability or aggressive violent temper outbursts.

Furthermore, this condition can also be worsened by inappropriate treatment. Bipolar disorders require a mood stabilizer, and are worsened by antidepressants; antidepressant treatment has been associated with increased risk of drug-induced mania[19]. Long-term course of the illness might also be worsened by the induction of treatment-resistant rapid-cycling episodes [20]. It seems likely that bipolar disorder type II with milder exaltation episodes (hypomania) may be at a higher risk of misdiagnosis than unipolar major depressive disorder, and mismanaged with antidepressants, resulting in a rapid-cycling course (more than 4 episodes per year).

Clinical guidelines for treating bipolar disorders clearly recommend careful diagnosis when focusing on any type of depressive episode, and suggest avoiding antidepressant treatment except in the brief treatment of severe acute bipolar depression, and in conjunction with a mood stabilizer [21].

This issue is directly linked to the potential violent behavior induced by antidepressants. Antidepressant agents can trigger mood changes in undiagnosed bipolar patients resulting in agitation and disinhibition, and such effects may lead to both suicide and violence. Antidepressant-induced mania is often characterized by admixtures of manic and depressive symptoms, and this mixed feature can provide suicidal ideation. Moreover, impulsivity increases during manic phases, contributing to the emergence of impulsive behavior [22].

Beyond the possible misdiagnosis with bipolar disorders, others diagnoses such as eating or anxiety disorders could be overlooked in young people, and antidepressants are not the first-line treatment in such conditions.

Beyond the Possible Problem of Misdiagnosis, Some Types of Depression are Worsened by Antidepressants

The DSM-IV criteria [23] defining major depression remain in fact very similar to those employed during 19th century, when pharmacotherapy did not exist and the description of depressive phenomenology was typically restricted to profoundly depressed patients. Currently, a large number of patients are diagnosed as depressed because they complain of sadness, however it is not clear whether they should be considered as depressed. They may certainly have severe depressed mood that deserves attention, but do all of these patients suffer from the same illness, requiring the same medication? Major depressive episode is a very broad construct and includes many clinical subtypes. However, there is only one description in current classifications (DSM-IV or CIM 10) to define the Major Depressive Episode. At least one of the symptoms is either depressed mood or loss of interest or pleasure that must be present for more than two weeks. In addition, four or more symptoms may be associated during this period of time, but some items show opposite changes: significant weight loss or weight gain in relationship with a decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation. Other symptoms are more linked to pessimistic or retarded cognition such as: feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate or recurrent thoughts of death or suicidal ideation. Thus, criteria for Major Depressive Episode in the DSM-IV are broad enough to include very different types of depression, and there is no means of defining these subtypes. Neurobiological disturbances underpinning depression characterised by cognitive and motor retardation and hypersomnia are most probably different from those in a depressive state associated with agitation and insomnia. However, the same therapeutic strategy is currently recommended for both.

Recently, extensive literature has been published in this area, suggesting new definitions for agitated or mixed depression, based on the coexistence of a major depressive episode and hypomanic symptoms such as motor agitation, intense inner tension, racing or crowded thoughts [24-28]. These authors have suggested that, when these states are treated with antidepressants, adverse outcome with increased agitation, panic attacks, increased risk of suicide and manifestations of psychotic symptoms might be induced. Moreover, some types of antidepressant-resistant depression may belong to this category and better respond to mood stabilizers or atypical antipsychotics [29,30]. For Akiskal, patients presenting with this mixed depression must be reconsidered as bipolar patients rather than unipolar, thus antidepressant should be avoided in these cases. Moreover, in a recent therapeutic trial, an atypical antipsychotic (olanzapine) alone or in association with an antidepressant (fluoxetine) resulted in a significant improvement in bipolar depression versus placebo group [30]. Thus, depressive states are not homogeneous and might have different patterns of response to treatment.

Beyond the debate on distinguishing unipolar and bipolar disease, reports that antidepressant use can be associated with an increase in suicidal thoughts and behavior have resulted in the public health advisory issued by the U.S. Food and Drug Administration (FDA). Among the warning information contained in the advisory, health care providers should carefully evaluate the emergence of an Activation Syndrome that may be a signal of worsening depression. The symptoms of this syndrome are: anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, severe restlessness, hypomania and mania [31].

Is there a Need for Better or More Varied Definitions of Depression?

Bauer [32] and McElroy and colleagues [33,34] have suggested that a dimensional approach could be useful to better classify mood states with an admixture of manic and depressive symptoms. Thus, we have developed a visual analogical scale assessing several potential dimensions, including emotion, cognition, motor, motivation and sensory functions. In this scale, emotions are not defined as a function of their "tonality" (e.g., euphoria, irritability, sadness, anxiety…) but in terms of the intensity of emotional reactivity (intensity of affect) that is probably more relevant to the disease process with regard to its neurobiological substratum. As previously shown, manic and mixed states are better defined by emotional hyper-reactivity, meaning that patients feel emotions with a greater intensity and depending on the environmental context, rather than by the tonality of affect, that tends to fluctuate [35]. Using this scale we have shown, in a preliminary study, that two types of bipolar depression can be distinguished [36]. One is characterized by an inhibition in all dimensions: emotional hypo-reactivity, cognitive and motor retardation, decrease of motivation and hypo-sensoriality. By contrast, the second type is characterized by a sub-excitation on all dimensions including an emotional hyper-reactivity. The main tonality of affects is sadness as in the depressive state with retardation, but in this case, sadness is associated with irritability, anxiety, panic attack, and sometimes bursts of exaltation. These emotions have a high lability but the global tonality is "dark" and associated with suicidal ideation. Many symptoms are common with the Activation Syndrome. It turns out that some of these depressions occurred spontaneously while some were triggered by antidepressants. Unfortunately, these two types of depressive states are not distinguished by current classifications and both respond to the criteria for a Major Depressive Episode. Thus, most of the depressive states worsened by antidepressant are considered as resistant depression requiring a change in the class of antidepressant, or an association of antidepressants or electroconvulsive therapy. Some preliminary data seems to indicate that these "resistant depressive states" might be improved by low doses of anti psychotics which act on the emotional hyper reactivity [36].

CONCLUSION

The fact that depressive states could be worsened by antidepressants implies that the concept of depression needs to be rethought. There are probably distinct types of depressive states with different therapeutic responses. Although, common sense leads us to use sadness as the hallmark of a depressive state, a more refined definition based on the amplitude of emotional reactivity is more efficient for defining subtypes of depression and for predicting the response to treatment. Moreover, the development of a new classification system is required in order to reduce the heterogeneity of depression representing a major impediment to elucidating the genetic and neurobiological basis of this common illness [37].

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