REVIEW ARTICLE

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Use of Selective Serotonin Reuptake Inhibitors in Children and Adolescents

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Contents

Abstract

Depression is a serious condition, associated with considerable morbidity and mortality; selective serotonin reuptake inhibitors (SSRIs) were commonly used in its treatment in child and adolescent psychiatry until recently. In the wake of the recent UK Committee on Safety of Medicines (CSM) advice, we conducted a rapid review of current available information on SSRIs and suicidality (suicidal ideation, self-harm and suicide attempt) in children and adolescents from clinical trials and epidemiological studies. There is insufficient safety information from the randomised controlled trials to confirm a definite association between SSRIs and suicidality. Furthermore, analysis of suicide and antidepressant prescribing trends in three countries and a large case-control study do not support the hypothesis that there is a link between use of SSRIs and death caused by suicide. Regulatory agencies and the media should have strict guidelines for the management of information relating to the treatment of this condition so that clinicians can make properly informed decisions.

We suggest clinical guidelines for managing depression in children and adolescents. SSRIs should not be considered for use as first-line treatment in mild or moderate depression of childhood, where psychological interventions such as cognitive behaviour therapy or interpersonal therapy are the mainstay. SSRIs should be considered when there is severe depression that does not respond to psychological interventions; when the child is suicidal and is admitted as an inpatient, is severely depressed or has bipolar depression despite adequate doses of mood-stabilisation agents; or when the child or family prefers pharmacotherapy to psychological interventions and gives informed consent. Local bodies of clinicians or peer groups should agree protocols and acceptable guidelines, taking into consideration the type of patients being assessed, the availability of nonpharmacological intervention, and the benefit-risk ratio of the pharmacological intervention. It is important that parents (and patients when possible) be given accurate information regarding the current controversy over SSRI prescribing. More research into the use of SSRIs in childhood depression is urgently required.

In June 2003, a warning was issued by the UK Committee on Safety of Medicines (CSM) against the use of paroxetine in children.[1] Subsequently the CSM issued a wider warning and recommended that venlafaxine (a serotonin and norepinephrine reuptake inhibitor) and none of the remaining selective serotonin reuptake inhibitors (SSRIs), except fluoxetine, be used in patients younger than 18 years.[2] Prior to the CSM advice, sertraline was the only SSRI licensed for use in children, for obsessive-compulsive disorder (OCD) in those aged 6 years and older; SSRIs and venlafaxine were mostly prescribed off label to depressed children. Following the regulatory actions of the CSM, the US FDA issued a recommendation to encourage close observation of adult and paediatric patients treated with these agents for worsening depression or the emergence of suicidality.[3]

Since then, many articles have been published debating the topic. The objective of this rapid review is to summarise some of the information provided by different sources and to discuss the way such information should be communicated to clinicians. We also share our clinical guidelines for prescribing SSRIs in childhood depression.

1. Rapid Review of Published Data

1.1 Reanalysis of Clinical Trial Data

We have summarised the data from different sources in table I, based on data from randomised controlled trials (RCTs).[2,4-11] The original data of the unpublished studies were not available; therefore it is necessary to use summary data from the CSM review. On the basis of the current RCT data, we agree with the Medicines and Healthcare products Regulatory Agency (MHRA) that fluoxetine is the only SSRI that has been demonstrated to have some clinical efficacy in children and adolescents with major depressive disorder; however, it should be noted that there was also a large placebo effect in all the RCTs.[12]

The data from the RCTs are not sufficient to allow any conclusion to be drawn about a link between suicidality (including suicidal ideation, self-harm and suicide attempt) and use of SSRIs and venlafaxine. Table I shows that there was no death due to suicide in any of the studies, nor was there a statistically significant increased suicidality rate compared with placebo in any of the RCTs.

The data published by the US FDA (table II)[13] showed that most RCTs reported that SSRIs had higher rates of 'possibly suicide-related' event and 'suicide attempt event' than placebo. Although these data are not adequate to confirm a link between suicidality and use of SSRIs, they signal that this issue requires further investigation.

1.1.1 Limitation of the Data

If it is assumed that the suicidality rate is 3.7% for a non-fluoxetine SSRI and 2.5% for placebo,[14] at least 3400 patients would be required receiving a non-fluoxetine SSRI and 3400 receiving placebo

Table I. Summary of randomised controlled trial (RCT) data in major depressive disorder (MDD) and obsessive-compulsive disorder (OCD) in children and adolescents

Parameter	Fluoxetine	Sertraline	Citalopram	Paroxetine	Venlafaxine
Licensed indications in children and adolescents in the US and UK	MDD in US; OCD in US	OCD in US and UK	None	None	None
Efficacy in MDD in children and adolescents	No. of studies: three[a] Age: 7–18y 177 pts (AD) 177 pts (PL) One small study did not show statistically significant results[4] Two studies showed some statistically significant results[5,6]	No. of studies: two Age: 6–17y 185 pts (AD) 179 pts (PL) Two studies combined data showed marginally statistically significant results in some parameters;[7] however, individual studies did not yield statistically significant results[2]	No. of studies: two Age: 7–18y 213 pts (AD) 205 pts (PL) One study showed only one parameter improved[8] One study showed no difference between AD and PL[2]	No. of studies: three Age: 7–18y 376 pts (AD)[b] 282 pts (PL)[b] One study showed some secondary outcome parameters marginally improved in a comparison between AD and PL[9] Two other studies showed no difference but no details of statistical tests were reported[2]	No. of studies: three[c] Age: 6–18y 189 pts (AD) 185 pts (PL) No statistically significant results[2,10]
No. of pts who died by suicide	None	None	None	None	None
Rates of suicidality[d] in AD and PL groups[11]	AD: 3.6% (9/249); PL: 3.8% (8/209);[ae] p = 0.9	AD: 2.7% (5/189); PL: 1.1% (2/184); p = 0.45	AD: 8.9% (19/205); PL: 7.3% (15/213);[f] p = 0.4	AD: 3.7% (14/378); PL: 2.5% (7/285);[b] p = 0.5	AD: 2.0% (3/169); PL: 0% (0/165);[c] p = 0.25

a Simeon et al.[4] trial excluded from CSM review.[2]

b Discrepancy between CSM review[2] and published article(s).

c Mandoki et al.[10] trial excluded from CSM review.[2]

d Suicidal ideation, self-harm and suicide attempt.

e Rates from OCD RCTs.[4-6]

f Rates from CSM review.[2]

AD = antidepressant; **CSM** = Committee on Safety of Medicines; **PL** = placebo; **pts** = patients.

Table II. Data published by the US FDA on suicidality.[13] Risk (%) and risk ratio for events classified as 'possibly suicide-related' and 'suicide attempts' in paediatric studies of major depressive disorder (all subjects; on-therapy data)[13]

Drug/study number	Possibly suicide-related			Suicide attempts		
	drug (%)	placebo (%)	risk ratio	drug (%)	placebo (%)	risk ratio
Paroxetine/329	6.5	1.1	5.9	5.4	0	
Paroxetine/377	3.9	4.2	0.9	3.9	4.2	0.9
Paroxetine/701	1.0	1.0	1.0	1.0	1.0	1.0
Fluoxetine/HCCJ	0	5.3		0	5.3	
Fluoxetine/HCJE	3.7	3.6	1.0	0.9	1.8	0.5
Fluoxetine/X065	4.2	4.2	1.0	4.2	0	
Sertraline/A050-1001	4.1	0		1.0	0	
Sertraline/A050-1017	2.2	2.2	1.0	2.2	2.2	1.0
Venlafaxine/382	6.25	1.18	5.3	2.5	1.18	2.1
Venlafaxine/394	7.84	0		1.96	0	
Citalopram/CIT-MD-18	1	2	0.5	1	1	1.0
Citalopram/94404	13	8	1.6	13	8	1.6

(95% CI and 80% power) to have sufficient sample size to detect statistical differences. There are insufficient data to draw conclusions at present. In a recent systematic literature review the authors also agreed that the number of patients included in their review is unlikely to have sufficient power to detect potential risk of suicide.[15] However, we acknowledge that it would be difficult to recruit such numbers of children and adolescents with depression into RCTs.

Interstudy variability in the definition of suicidality makes it difficult to determine the true frequency of suicidal behaviour and ideation even though an increase was observed. It is not clear if all of the data released by the US FDA in table II correspond with studies reviewed by the CSM, creating some doubt as to whether a full review of all the available data has been conducted. The data from the CSM review were compared with the FDA data and some differences were noted; for example, in the Citalopram Study 94404 (Citalopram Study 2 of the CSM review), the SSRI has a 'possibly suicide-related' rate of 16/121 (13.2%), whereas the CSM review states that the rate is 18/124 (14.5%). These discrepancies are minor and may be due to summation of data, but they may have an effect if the study population is small. Also, the discrepancies could lead to lack of confidence in the reviews of unpublished data, supporting the view that all trial data should be in the public domain.

1.2 Comparison of Psychological and Pharmacological Interventions

1.2.1 Comparison of Fluoxetine and Cognitive Behaviour Therapy in Adolescent Depression

Initial treatment of major depressive disorder in adolescents may include cognitive-behavioural therapy (CBT) or an SSRI. As little is known about their relative or combined effectiveness, March et al.[16] evaluated four treatments among adolescents with major depressive disorder. The study was a randomized controlled trial of a volunteer sample of 439 patients aged 12–17 years with a primary *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, diagnosis of major depressive disorder. The interventions consisted of 12 weeks of (i) fluoxetine alone (10–40 mg/day); (ii) CBT alone; (iii) CBT with fluoxetine (10–40 mg/day); or (iv) placebo (equivalent to 10–40 mg/day). Placebo and fluoxetine alone were administered double blind while CBT alone and CBT with fluoxetine were administered unblinded. Rates of response were 71.0% for fluoxetine with CBT, 60.6% for fluoxetine alone, 43.2% for CBT alone and 34.8% for placebo. On the Clinical Global Impressions improvement responder analysis, the two fluoxetine-containing conditions were statistically superior to CBT and to placebo. Compared with placebo, the combination of fluoxetine with CBT was superior to fluoxetine alone and CBT alone, with fluoxetine alone being superior to CBT alone. However, replication of this finding will be needed in the future.

The investigators reported that clinically significant suicidal thinking was present in 29% of the sample at baseline. This improved significantly in all four treatment groups, with the fluoxetine with CBT group showing the greatest reduction. Seven (1.6%) of 439 patients attempted suicide but there were no completed suicides. Five and a half percent experienced a suicide-related adverse event. Rates of harm-related events between the four groups were not significantly different. However, there was an elevated risk of harm-related events for the two fluoxetine groups compared with the non-fluoxetine groups (odds ratio 2.19). Subgroup analysis showed a protective effect of CBT when combined with fluoxetine on suicide and harm-related adverse events. March and colleagues[16] concluded that the combination of fluoxetine with CBT offered the most favourable treatment for adolescents with major depressive disorder, taking into account the benefit and risk considerations.

1.3 Epidemiological Data

1.3.1 Analysis of Secular Trends

The Task Force on SSRIs and Suicidal Behavior in Youth of the American College of Neuropsychopharmacology[17] has used epidemiological data to argue against a link between suicidality and the use of SSRIs. They used the technique known as 'analysis of secular trends'. This technique examines trends in an exposure that is a presumed cause of an adverse drug reaction (ADR) and trends in a disease that is a presumed effect of an ADR, testing whether these trends coincide. Vital statistics, such as mortality rates, are often used for these studies. A good example is the correlation between the introduction of isoprenaline (isoproterenol) and fenoterol inhalers and increase in mortality from asthma in New Zealand.[18]

The Task Force analysed WHO data[19] and has suggested that there was an average 33% reduction in suicide rate of youth (age 15–24 years) across at least 15 countries over the past 14 years.[17] The decline in youth suicide rates coincides with significant increases in the prescription of antidepressants, mostly SSRIs, to adolescents.[20-23] Three groups of researchers from Finland, the US and Sweden have demonstrated that the increase in prescription of antidepressants coincides with the reduction in suicide mortality rates in their individual country.[24-26] These data do not support the hypothesis that there is a link between use of SSRIs and death caused by suicide.

Analysis of secular trends provides indirect evidence against the hypothesis of association of suicide mortality and use of SSRIs. However, these studies lack data on individuals, implying that it is not possible to control for confounding factors and that the results may be open to misinterpretation.[18]

Ohberg et al.[26] also reported that, although suicide mortality was decreasing, suicides by use of antidepressants showed an upward trend. Hence, the reduction in suicide mortality is not necessarily due to the effectiveness of SSRIs; it could be explained by lower toxicity than experienced with tricyclic antidepressants.[27]

Because of the aforementioned limitations, it is difficult to prove that the massive increase in antidepressant prescribing has had any objective and positive effect on the health of populations.[28]

Finally, there are some potential conflicts of interest with several members of the task force: some are authors for the RCTs conducted in children and adolescents and are affiliated with the pharmaceutical companies that produce SSRIs.[17]

1.3.2 Matched Case-Control Study of Primary Care Database

Jick et al.[29] investigated the association of suicide with the use of fluoxetine, paroxetine and amitriptyline in UK general practice. They found that the risk of suicidal behaviour after starting antidepressant treatment was similar among users of amitriptyline, fluoxetine and paroxetine compared with the risk among users of dosulepin (dothiepin). The risk of suicidal behaviour was increased in the first month after starting antidepressants, especially during the first 1–9 days. A possible small increase in risk (bordering statistical significance) among those starting the newest antidepressant, paroxetine, was of a magnitude that could readily be due to an uncontrolled confounding factor, such as the severity of the depression. On the basis of limited information, Jick et al.[29] also concluded that there was no substantial difference in effect of the four drugs on people aged 10–19 years. Particularly, no fatal suicide attempts in those aged 10–19 years were found.

1.4 Discussion

It is increasingly accepted that depression not only occurs in adults but also in adolescents and children. There is no doubt that adolescent depression is common and that it causes much morbidity and some mortality. There is also no doubt that clinicians would welcome a range of effective treatment options in a condition that is common, serious and sometimes difficult to treat.

2. Hypothesis of Suicidal Behaviour and Selective Serotonin Reuptake Inhibitors (SSRIs)

Suicidal ideation and suicide attempt have been described in adult patients treated with fluoxetine. For example, Teicher et al.[30] presented six case reports of depressed patients aged 19–62 years who developed suicidal preoccupation after 2–7 weeks of fluoxetine treatment. The self-destructive thoughts persisted or even worsened temporarily after fluoxetine was discontinued. They resolved completely a mean of 87 (range 60–106) days after stopping the fluoxetine. The investigators stated that the risk of this violent suicidal ideation was small and estimated it as 3.5% (95% CI 1.3%, 7.5%) in their patients receiving fluoxetine. Their conclusion was that patients should be warned that this medication does not always work, that some patients may feel worse and that a few have developed suicidal thoughts.[30]

Since these early reports, the debate about suicidality and SSRIs in adults has continued. For example, Healy and Whitaker[31] have argued both from a meta-analysis of RCTs giving an odds ratio of 2.4 (95% CI 1.6, 3.7) for the excess of suicidal acts with SSRIs compared with placebo and from epidemiological studies that SSRIs appear to be associated with an increased risk, whereas the recent review of the data by Lapierre[32] concludes that the current evidence does not support the hypothesis that SSRIs increase suicidality.

Suicidal or self-injurious ideation or behaviour may also be seen in adolescents treated with SSRIs for conditions other than depression. King et al.[33] reported six cases (age 10–17 years, three boys and three girls) out of 42 who were treated with fluoxetine for OCD. However, at least four of these young people were also depressed before or during treatment. In four cases the self-injurious ideation or behaviour appeared in the first 2 months, but in the other two it appeared 6 months or more after commencing treatment. One of the adolescents developed intense suicidal ideation about 1 week after increasing the dosage to 60 mg/day, having been treated for almost 1 year on lower doses without these symptoms. These uncontrolled reports must be interpreted with caution.

SSRIs do have adverse effects of stimulation, increased anxiety and sleep impairment in the early phase of treatment,[34-36] which may increase suicidal ideation or acts. Worsening anxiety in the initial period of prescribing an SSRI to depressed adults was recognised when SSRIs were initially introduced as antidepressants, and many clinicians were co-prescribing a benzodiazepine (with the SSRI) for the first 2–3 weeks to overcome this.[37] Smith et al.[37] suggested that augmenting an SSRI with a benzodiazepine in the first 3 weeks of SSRI treatment may partially suppress SSRI adverse effects, may increase compliance and could possibly reduce the risk of suicide. However, this strategy has not been adopted in child mental health.

One of the common clinical features of depression is anergia. Some people who are depressed may be so lacking in motivation that they cannot even summon the energy to commit suicide. It has been widely accepted for many years that the early phase of treatment of such patients should be viewed as a time of great risk because the previously anergic patient may summon just enough energy to think about and actually commit suicide.[38,39] Careful monitoring by the clinical team is mandatory. If all these factors are accepted, the evaluation of suicidality in patients treated for depression needs to be carried out very carefully. In particular, patients should be monitored carefully in the early stages of treatment and followed up for a sufficient length of time; no early conclusions should be drawn from a temporary worsening of their state of well-being.

Unfortunately, the data available from the CSM are insufficient to confirm or refute the hypothesis that SSRIs give anergic patients just enough energy to attempt or commit suicide in the early phase of treatment. Detailed analysis of the original clinical trial data would be needed to investigate this hypothesis.

SSRIs such as paroxetine are mostly metabolised by cytochrome P450 2D6. It has been reported that clearance is greater in children aged 6–17 years than in adults aged 20–30 years; therefore children may require higher than normal adult doses per kilogram of bodyweight.[40] Whether these factors have any clinical implications with regard to efficacy and safety still needs to be determined.

Leeder[41] also pointed out that it is difficult to know whether the symptoms of suicidality represent unintended consequences of pharmacological modulation of maturing neurochemical networks (receptor-signal transduction pathways) that occur as the brain develops or whether the symptoms represent developmental differences in the nature of depressive illness between children and adults. Further developmental and pharmacogenomic research is required to answer these questions.

3. Role of Drug Regulatory Agencies and the Media

What should the role of the medication regulatory agencies and the media be in situations such as this? Government agencies have a duty to inform, so that clinicians can make decisions on the best information available. However, they should direct clinicians only if they are confident about the facts and, in particular, about their benefit-risk analysis. Such an analysis should always include a careful statistical evaluation of the evidence, which should be made available to clinicians. Clinicians should have access to the unpublished data that pharmaceutical companies make available to committees such as the CSM. However, because of confidentiality clauses, such information is generally unavailable to clinicians. This may make it difficult for clinicians to comprehend decisions made by the committees. Without such information, clinicians are not in a position to make properly informed decisions.

Unless there are compelling reasons for not doing so, the regulatory agency should always emphasise that decisions about individual patients using psychotropic medication should be based on clinical grounds. This implies that a statement along the lines of the following should usually be included: "No patient should stop medication without seeking medical advice. If the doctor and patient agree that the medication has been of benefit or is likely to be of benefit, they may agree that it should be continued". The regulatory agencies should also make sure that telephone advice is available to clinicians. Such advice can then be quoted to families who may be uncertain about how to interpret their own particular situation. One of the authors called the telephone number given in a recent communication from the regulatory agency on this matter on two occasions only to find that the person answering the telephone had no idea what it was about and did not know how to redirect the call. The agency subsequently apologised.

Finally, the media should be aware of the fact that if they do not choose their words carefully when reporting on these matters they may actually be responsible for increasing morbidity or mortality of patients. The recommendation not to treat young people under the age of 18 years with one of the newer antidepressant drugs was reported on the front page of at least one of the major daily newspapers in the UK and was also featured in the television news. This was not accompanied by a statement of the type recommended earlier, emphasising that some patients may benefit from the medication and that decisions should always be made in consultation with the responsible doctor.

A more difficult but nevertheless important question relates to the placebo effect, which is large in the treatment of depression and occurs in addition to any direct chemical benefit. The choice of words used by the media can almost certainly have a negative placebo effect. Not only is the positive additional placebo effect of the medication removed by unnecessarily damning reporting but the medication might actually be viewed as harmful and swing a person into a depressive phase. How much family morbidity and how many suicides from inadequately treated depression have occurred as a result of the inappropriate choice of words in the media? We may never know the answers to these important questions but there can be no doubt that the media should be made aware of these issues and exercise great caution in their reporting of matters such as this.

4. Clinical Guidelines for Using SSRIs in Childhood Depression

Since the announcement of the CSM's advice, we have been asked many times by clinicians and pharmacists about policy on the use of SSRIs in children. On the basis of our experience and understanding of available information, we have developed our own local guidelines. We wish to emphasise here that the following guidelines are only for reference purposes; it is important for individual organisations to develop their local guidelines according to their local policies such as risk management policy and primary and secondary shared care policy.

4.1 Our Local Guidelines

- Psychological treatments such as CBT, interpersonal therapy or other psychological interventions should be used as first-line treatment whenever possible, especially for mild or moderate depression. The only head-to-head comparison of psychological and pharmacological interventions in depressive disorders in adolescents suggests that a combination of fluoxetine and CBT is superior to fluoxetine or CBT alone and that fluoxetine was superior to CBT.[16] However, it is reported that the fluoxetine-treated groups showed greater harm-related events. Therefore, the risk/benefit ratio of pharmacological intervention would suggest that ideally combined fluoxetine and CBT treatment should be used, but if single treatments were to be considered, medication should be reserved for managing severe episodes of depression. However, there has been no published research to date that has taken severity of depression into account when looking at response to depression and suicidality.
- When pharmacological intervention is being considered, fluoxetine should be prescribed as the first-choice SSRI (with sertraline and possibly citalopram being considered as second-line medication), where necessary.
- Parents, and the child where appropriate, should be informed about the current uncertainty and controversy regarding the use of SSRIs as part of the process of obtaining informed consent. This information should include a statement that a small proportion of patients may become worse, not better, and that if there is any suggestion that this is happening, the clinician should review the situation immediately.

4.2 Reasons for Starting an SSRI in Childhood Depression

Reasons for starting an SSRI in childhood depression should be as follows.

- 'Depressive episode – severe subtype without psychotic symptoms' (F32.2), according to the *International Classification of Diseases* – 10th revision (ICD-10).[42]
- 'Depressive episode – severe, with psychotic symptoms', i.e. delusions, hallucinations or depressive stupor (F32.3 from the ICD-10).[42]
- As an adjunct to psychological interventions when response has been inadequate to psychological intervention alone.
- Severe bipolar depression that persists despite adequate doses of mood-stabilising medication.
- When family and/or child refuses psychological interventions and gives informed consent for use of medication.
- If the patient is significantly suicidal, the use of SSRIs should be considered, with close supervision, possibly during a hospital admission.

4.3 Reasons to Attempt a Switch to Another SSRI Other Than Fluoxetine

The reasons to attempt a switch to another SSRI, other than fluoxetine, should be as follows.

- Lack of or inadequate response to a full dose of fluoxetine (up to 60 mg/day if necessary), for at least 6–8 weeks.
- Known intolerance to fluoxetine.
- The presence of a comorbid condition such as OCD or anxiety (with depression), which warrants the use of another SSRI that has been licensed for that condition (e.g. sertraline in childhood OCD).
- Previous response to another SSRI and parents (and/or child where appropriate) insisting on the use of the previous SSRI, despite being informed about the current issues around its prescription.

5. Conclusions and Future Directions

There is information from RCTs showing that fluoxetine is more effective than placebo in the treatment of severe depression in children; however, a strong placebo effect was observed. Fluoxetine in combination with CBT appears to be superior to fluoxetine or CBT alone. SSRIs should not be considered for use as first-line treatments in mild to moderate depression of childhood, where psychological interventions such as CBT or interpersonal therapy are the mainstay. SSRIs should be considered when there is severe depression that does not respond to psychological interventions, when the child is suicidal and is admitted as an inpatient or has bipolar depression despite adequate doses of mood-stabilisation agents, or when the child or family prefers pharmacotherapy to psychological interventions and gives informed consent. Whenever possible, SSRIs should be used in addition to psychological interventions.

Despite repeated reports of associations of increased harm-related events and SSRIs, there is insufficient safety information from the RCTs to draw any conclusions about a possible association between SSRIs and suicide, but there may be an association with harm-related behaviours. Analysis of trends in three countries and a large matched case-control study do not support the hypothesis that there is a link between the use of SSRIs and death caused by suicide.

Development of collaborative, global research networks into treatment of depression in children and adolescents will enhance identification of trends more quickly than research performed by single departments on small numbers of individuals. Research into the assessment and monitoring of treatment-emergent harm-related behaviours should be considered a priority.

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