SSRIs and SNRIs: A review of the Discontinuation Syndrome in Children and Adolescents

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Abstract

Objective: To review the occurrence, clinical relevance and characteristics of the discontinuation syndrome in children and adolescents who have been on a selective serotonin reuptake inhibitor (SSRI) or a serotonin/norepinephrine re-uptake inhibitor (SNRI) for various conditions as an update for physicians prescribing these medications in this population.
Method: An on-line literature search was done using MEDLINE, PubMed, CINAHL, PsychARTICLES, and PsychINFO with the following key words: selective serotonin reuptake inhibitors or SSRIs, serotonin/norepinephrine re-uptake inhibitors or SNRIs, discontinuation syndrome, pediatric or children or adolescents, occurrences and characteristics. **Results:** Not a single randomized placebo-controlled trial was found that addresses this condition solely in the child and adolescent population. A couple of papers written by the same authors indicate that children and adolescents taking an SSRI definitely experience discontinuation reactions that can be mild, moderate or severe when the medication is stopped suddenly or high doses are reduced substantially. Among the SSRIs paroxetine seems to be the worst offender and fluoxetine the least while sertraline and fluvoxamine tend to be intermediate. However, the most serious discontinuation reactions came from the SNRI venlafaxine. There was no study or reports found on citalopram, another SSRI that is commonly prescribed in children and youth. While the adult literature abounds with papers describing the different aspects of this condition including clinical features, diagnostic criteria, management and prevention, the limited information available to-date in children and adolescents indicate that the essential features of the discontinuation syndrome may not be significantly different than in adults. There were no specific characteristics identified relating to the child population. **Conclusion:** In considering the use of an SSRI in children, physicians must seriously weigh the not so clear benefits against the risks of adverse reactions including the discontinuation syndrome. The frequency and severity of this reaction seem dependent on the SSRI half-life and although children metabolize drugs much faster than adults the reactions to-date have been reported as similar. The use of fluoxetine with its long half-life appears safer in this respect with paroxetine and venlafaxine causing the most concerns. Patients and their families should be well informed of the risks of stopping the medication abruptly and instructed not to do so without consulting their physician. Physicians in Canada who are using these medications off-label in children need to be knowledgeable and vigilant about such adverse reactions. These could be avoided through adequate follow ups which will also ensure better adherence. They may benefit from this review even though the information comes mostly form the adult literature. More prospective studies are needed to clarify this issue and identify any specific features relating to the pediatric population.

Key words: *selective serotonin reuptake inhibitor, serotonin/norepinephrine re-uptake inhibitor, children, adolescents, discontinuation, adverse effects*

Introduction

The use of selective serotonin receptor inhibitors (SSRIs), in children and youth, has met with a lot of controversy since 2004. Some professionals do not feel they should be prescribed at all in this age group even as a last resort (Herxheimer & Mintzes, 2004) while others feel they should be used with caution only after failure of psychosocial and environmental interventions (Voysey, 2004). Anxiety disorders are referred to as the most common mental disorder in children affecting over 64,000 children in British Columbia alone (Waddell, Godderis, Hua, McEwan & Wong, 2004) and evidence-based treatment for anxiety, obsessive compulsive disorder and depression recommends a combination of cognitive behavior therapy and medication. This has been problematic for two reasons. First, in Canada, other than in specialized anxiety disorder clinics, the availability of well-trained cognitive behavior therapists in the public sector is fairly limited (The Provincial Strategy Advisory Committee for Anxiety Disorders, 2002). Second, Health Canada has to-date not licensed any SSRI for use in this population (British Columbia Ministry of Health Services, 2010) although in the United States fluoxetine, fluvoxamine and sertraline are

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approved for the treatment of obsessive-compulsive disorder by the Food and Drug Administration agency (FDA) and fluoxetine and escitalopram for treatment of depression (Ronsley, Elbe, Smith & Garland, 2010). In the absence of other management strategies physicians have limited choices and SSRIs are regularly prescribed in this country (Ronsley et al, 2010). Any such use in patients under 18 years of age is hence off-label (Voysey, 2004). Off-label use of these drugs in children is acknowledged to be an important tool for doctors who need to rely on their knowledge of patients and the drugs to prescribe them at their discretion (British Columbia Ministry of Health Services, 2010). Without an "officially approved" indication, educational activities have been few in this area, unlikely to be sponsored by the pharmaceutical industry. Physicians in Canada may not be receiving adequate information for proper use and monitoring of these medications in children. An older survey of 200 UK psychiatrists reported that 18% were not aware of the antidepressant discontinuation syndromes and 20% never informed or advised their patients routinely when ending treatment (Olver, Burrows & Norman, 1999). Although these numbers are likely to be lower at present, the fact that SSRIs are prescribed not only by psychiatrists but also by pediatricians and primary care physicians (Ronsley et al., 2010) indicates a need for better awareness of adverse events. Physicians should be aware that a good number of their patients stop taking an antidepressant medication after a few weeks of treatment. One study reported that 23 % of adults prescribed an SSRI discontinued medication at 4 weeks and 36.5 % within 3 months (Tanno, Ohira, Tsuchiya, Takeuci & Tanno, 2009). Another report indicated that approximately one half of patients discontinued antidepressant medication within 3 months (Simon, VonKorff, Wagner & Barlow,1993). Medications are more likely to be abruptly stopped by younger patients often without the knowledge of parents or the physician. The more side effects the medication has in the early phase of treatment the more likely it is to be discontinued abruptly (Himei and Takenhiko, 2006). For some SSRIs, any sudden withdrawal from the drug has been known to cause considerable distress and even impairment in functioning. With the ongoing concerns and controversy surrounding the use of SSRIs in children and youth it is all the more important for medicated children and their families to be fully informed of possible adverse effects sooner rather than later. The purpose of this paper is to provide an update of this fairly common but often missed adverse reaction referred to as the discontinuation syndrome by reviewing its main aspects with a focus on children and youth.

Methodology

An on-line literature search was done using MEDLINE, PubMed, CINAHL, PsychARTICLES, and PsychINFO with the following key words selective serotonin reuptake inhibitors or SSRIs, serotonin/norepinephrine re-uptake inhibitors or SNRIs, discontinuation syndrome, pediatric or children or adolescents, occurrences and characteristics. As only 2 papers were identified in the pediatric population written by the same authors (Diler, Tamam & Avci, 2000, Diler & Avci, 2002) an additional search was done using only the key words selective serotonin reuptake inhibitors or SSRIs, serotonin/norepinephrine re-uptake inhibitors or SNRIs, discontinuation syndrome, essential and diagnostic features. Numerous articles relating mainly to the adult population were obtained. They were reviewed for essential information on the discontinuation syndrome. Any clinical information bearing some relevance to the child and youth population was extrapolated. Appropriate references from various published articles were also identified and reviewed in a similar way. This is reflected in the information presented.

The Discontinuation Syndrome

General Features (SSRIs)

The discontinuation syndrome is a withdrawal type of reaction that an individual taking an SSRI over a period of time experiences whenever there is an abrupt cessation of the medication. The term discontinuation rather than withdrawal syndrome is favored to avoid any misconception about drug dependence or addiction (Haddad & Anderson, 2007) especially by highly anxious children and families. Antidepressant medications are not believed to be habit forming or addictive as they are not associated with drug–seeking behaviors (Coupland, Bell & Potokar, 1996) and have no clinically significant potential to cause dependence (Haddad, 2001). Discontinuation symptoms do also occur during rapid tapering of the medication especially if there is a substantial decrease in dosage. Symptoms also rapidly resolve upon re-starting the original SSRI (Haddad, 2001). All SSRIs have been implicated including fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram and lately escitalopram, although the respective reactions may not be of equal severity. It is important to note that this adverse effect has also been described with other types of antidepressants including tricyclics (TCAs) and serotonin /norepinephrine reuptake Inhibitors (SNRIs). It also occurs with other classes of psychotropic medication including antipsychotics and mood stabilizers (Schatzberg et al., 1997). Reasons for stopping medication suddenly include non-adherence for different reasons including side-effects, accidental (or deliberate) missing of a dose, routine (or abrupt) discontinuation following maintenance therapy, pregnancy, a superimposed medical illness, switching from an ineffective SSRI, drug holidays and the high cost of medication (Olver et al., 1999). Non-adherence to a medication is often related to its tolerability and a measure of tolerability is the discontinuation rate. Fluvoxamine has been associated with more side-effects and hence with the highest discontinuation rates during treatment (up to 70%

Table 1. (Compiled from various sources)

Drug	Mean half-life (Hours)	Range (Hours)	Active metabolite
Fluvoxamine	15.6	15-22	None
Paroxetine	21	21-24	None
Paroxetine CR	18	15-20	None
Sertraline	26	22-36	N-desmethylsertraline (2-3 times longer)
Escitalopram	30	27-32	None
Citalopram	35	35-37	None
Fluoxetine	96	81-144 hours	Norfluoxetine (4 -16 days)
Venlafaxine	5	3-13	O-desmethyl-venlafaxine (lasts 11 hours)
Duloxetine	12	8-17	None

within the first 2 months), followed by fluoxetine (45%) and sertraline (40%) in clinical trials (Ferguson, 2001). No added risk has been associated with gender (Himei & Okamura, 2006). This was confirmed by a retrospective chart review of 350 patients using SSRIs which showed no significant added risk associated with age, sex, or diagnosis (Coupland et al, 1996). However it tends to be more common in patients using higher dosages (Perahia, Kajdasz, Desaiah & Haddad, 2005). It is also reported that the longer the patient takes the medication the higher the incidence or severity of the discontinuation syndrome (Rivas-Vazquez, Blais, Johnson & Rey, 1999), but usually a plateau is reached with no further increase in incidence over time (Perahia et al., 2005). The shortest reported duration of treatment prior to a discontinuation syndrome developing is 5 weeks (Haddad, 1998). Discontinuation symptoms seem less likely when switching between antidepressants with similar pharmacodynamic profiles but can still occur (Haddad, 2001).

The Half-life issue

The severity of the discontinuation syndrome is not the same for each SSRI. It seems to be related to the drug's half- life. The shorter the half-life the quicker the drug will be eliminated and the more common is the discontinuation reaction (Coupland et al., 1996, Judge, Quail & Jacobson, 2002). To appreciate the impact of the different SSRIs it would be useful to be aware of their respective half-lives. Unfortunately data on the half-life of each SSRI are not readily available in children. Data from adult studies on the other hand indicate a wide range of values for each SSRI and can only be shown as approximations at the very best (Table 1).

Fluvoxamine seems to have the shortest half-life of all SSRIs and as such it would be expected to have a higher incidence or severity (greater number of symptoms) than paroxetine, and fluoxetine would have the least. However, many reports indicate that the most common or severe reactions occur with paroxetine, intermediate ones with fluvoxamine and sertraline and the least common or severe ones with fluoxetine. One randomized double blind placebo controlled study using a 5 day period of treatment interruption with placebo substitution reported that the worst symptoms occurred by the end of the fourth day. Paroxetine was associated with 13 symptoms out of a 17 item scale, 3 out of 17 for sertraline and up to the fifth day no symptoms for fluoxetine (Haddad, 2001). Also the half-lives of medications could be shorter in children as they metabolize drugs faster. This could mean a different presentation in children but no such difference was documented in the case of 6 children, one of which was on sertraline, 3 on paroxetine and 1 on fluvoxamine (Diler & Avci, 2002). It has been reported further that the elimination half-lives for sertraline and desmethylsertraline are similar to adult values with no pharmacokinetic differences seen after parameters were normalized for body weight (Alderman et al., 1998). At the same time it is also mentioned that the average half-lives of paroxetine in children after a 10 mg dose is 11.1 hours, nearly half that of the adult which could make them more vulnerable to experience discontinuation symptoms within a short time (Diler et al., 2000). This does not seem to be quite the case and more clarifications are needed for a better understanding of the half-life issue and its implications.

Clinical Features

Onset

In adults, the onset of symptoms occurs within 1-3 days of stopping the medication and in the majority of cases not later than one week with practically no discontinuation symptoms occurring beyond 2 weeks (Black, Shea, Dursun & Kutcher, 2000). One exception is fluoxetine where symptoms may be delayed likely due to its long half-life (Haddad, 2001), sometimes up to 4 weeks. In the case of 6 children taking different SSRIs for 3-6 months, all experienced discontinuation

Table 2. (Compiled from different sources)

Nervous system	Somatic	Gastrointestinal	Sensory	Sleep-Disturbance	Psychological/ affective
Dizziness	Lethargy	Nausea	Numbness	Insomnia	Irritability
Light-headedness	Fatigue	Vomiting	Tingling	Vivid dreams	Dysphoria
Vertigo (feeling faint)	Headache	Diarrhea	Electric/shock-like sensations	Nightmares	Low mood
Tremor	sweating	Abdominal discomfort	Blurred vision		Anxiety
Ataxia (gait instability)	Myalgia	Abdominal cramps	Paresthesia		Nervousness, agitation
Visual disturbances	Flu-like symptoms	Abdominal distention			

symptoms within 1-5 days of stopping the medications (Diler & Avci, 2002). This is no different than the adult population.

Incidence

The rate of discontinuation syndrome varies with the particular SSRI involved. It is generally quoted as 25% but is higher for SSRIs with shorter half-lives. Paroxetine has been associated with more frequent discontinuation symptoms than the other SSRIs. The rate of discontinuation with paroxetine has been reported at 34.5% compared to placebo at 13.5% in a 12 week double-blind placebo-controlled study (Haddad, 2001). An analysis of the rate of discontinuation syndrome in the United Kingdom, expressed per 1000 prescriptions written, revealed that the rate for paroxetine was over 100 times higher than fluoxetine and 10 times higher than sertraline or fluvoxamine (Haddad, 2001). Symptoms even occur during tapering of paroxetine (Black et al., 2000). It is also important how the information is gathered. On paroxetine and sertraline at least 1 in 3 patients spontaneously reported one or more discontinuation symptoms (Haddad, 2001). However, when the information was actively solicited by the physician the incidence for the same two SSRIs increased to 2 out of 3 patients (Haddad, 2001). The rates also seem to differ in different studies. A comparison study reported the incidence of the discontinuation syndrome as 20% for paroxetine, 14% for fluvoxamine, 2.4% for sertraline and 0% for fluoxetine (Coupland et al., 1996). Yet another study reported a frequency of 42% in the paroxetine group and 9% in the fluoxetine group (Bogetto, Bellino, Revello & Patria, 2002). A randomized controlled trial comparing 3 SSRIs found the highest incidence with paroxetine (66%) followed by sertraline (60%) and the lowest incidence (14%) was with fluoxetine (Warner et al, 2006). Discontinuation symptoms for citalopram have been reported as mild. A study conducted with citalopram reported practically no observed discontinuation symptoms upon abrupt discontinuation (Rivas-Vazquez et al., 1999). Another study reported significantly fewer discontinuation symptoms with escitalopram than with paroxetine and venlafaxine XR (Baldwin, Montgomery, Nil & Lader, 2007). Such figures are not available in children but it is likely that the incidence would be highest with paroxetine and lowest with Fluoxetine with the other SSRIs somewhere in between, similar to adults.

Symptomatology

More than 50 different SSRI discontinuation symptoms have been identified (Haddad, 1998). Some patients present with only one or two symptoms while others present with numerous symptoms. The most common ones can be divided into the following clusters (Table 2).

The number of symptoms in adults varies from 1-12, sometimes more, per patient with dizziness being the most common symptom (Black et al., 2000). Dizziness has been described in more than 60% of cases, followed by nausea (almost 40%), lethargy and headache (Haddad, 1998, Bogetto et al., 2002). The most common symptoms reported in children are: dizziness, lightheadedness, drowsiness, poor concentration, nausea, headache and fatigue. Dizziness seems to be the most common symptom in both children and adults (described as feeling spaced out, stoned or drunk). No cardiac symptoms or arrhythmias have been reported as part of the SSRI discontinuation syndrome (Haddad, 2001). Another common symptom in adults is paresthesia described as burning, tingling, numbness or electric shock feelings usually in the upper half of the body or proximal lower limbs (Olver et al., 1999).

Diagnostic Criteria

To facilitate early identification of the SSRI discontinuation syndrome the following set of diagnostic criteria has been proposed (Black et al., 2000):

- Two or more symptoms occurring within 1-7 days of stopping the medication or reducing the dosage;
- After at least 1 month's use;
- Symptoms causing clinically significant distress and impairment in functioning;
- Symptoms are not due to a general medical condition or recurrence of a mental disorder.

One problem with this proposal arises with fluoxetine due to reports of a delayed reaction with symptoms not appearing until 4-6 weeks after stopping the medication (Haddad, 2001). There are no specific operational criteria for children at this time and no reason to believe that they could not be diagnosed using the above diagnostic criteria.

Severity

The discontinuation syndrome following SSRI use can be classified as mild, moderate and severe. It is often missed because most reactions are fairly mild and of short duration. In a number of cases the reactions can also be moderate to severe, last longer and have significant morbidity (Haddad, 2001). Symptoms like headache, ataxia, and insomnia can cause distress and interfere with the child's functioning enough to adversely affect adherence to future antidepressant use. The duration of adverse symptoms is usually brief. Untreated, most symptoms spontaneously resolve within 1-2 days but can take up to a week. Symptoms tend to disappear within 2 weeks. In a few cases they can be more severe and can last up to 3 weeks even beyond. The physician has to be vigilant so as not to miss those cases. Diagnosed early they can be easily treated to avoid distress and disability. The severity of the reaction is also influenced by the SSRI used. Fortunately in the treatment of children and youths with both anxiety disorders and depression the present guidelines for the use of SSRIs recommend fluoxetine as first line medication (Garland, Virani & Kutcher, 2009, Impact BC, 2010). As a result, if a majority of children are treated with fluoxetine, they will experience a milder reaction than those treated with sertraline or paroxetine (Haddad, 2001). Hence discontinuation reactions in the majority of children may not be a major concern. Still some may have intolerable side effects to fluoxetine while others may respond better to paroxetine such as for Social Anxiety Disorder and fluvoxamine or sertraline for Obsessive Compulsive Disorder. Many of these youth may also have other co-morbidities including poor executive functioning and poor working memory. They are the ones who need to be monitored for abrupt cessation of medication and may experience severe discontinuation reaction.

Management

In a majority of the cases no active treatment is required for the discontinuation syndrome as symptoms are mild. With reassurance the symptoms usually resolve spontaneously often within a week. For moderate symptoms, if further SSRI treatment is no longer required, the treatment is mainly symptomatic and aimed at alleviating the disturbing symptoms. Severe symptoms arising when the medication is discontinued can usually be alleviated by the re-introduction of the SSRI followed by a gradual tapering of the medication over a longer period of time. Similarly symptoms occurring while tapering an SSRI can be managed by increasing the dose again followed by a more gradual and longer period of dose reduction. In some cases where tapering of the SSRI is unsuccessful due to the continuing re-emergence of symptoms it is recommended to overlap with an SSRI with a longer half-life like fluoxetine, taper and discontinue the offending SSRI and finally slowly taper and discontinue the fluoxetine. With treatment most symptoms resolve fairly completely within 24-72 hours.

Currently there is no set rule regarding the rate of taper. For example tapering paroxetine at a rate of 5 mg every 2-4 weeks did not cause re-emergence of symptoms (Himei & Okamura, 2006). A more cautious taper advocated consists of decreasing the dosage of the SSRI by one-quarter every 4-6 weeks (Haddad, 2001). The British Columbia guidelines and protocols advisory committee on anxiety and depression in children and youth recommends tapering off particularly slowly over 1-2 months by approximately 5 mg per reduction for some SSRIs (British Columbia Ministry of Health Services, 2010). Such a regime would apply mostly to those SSRIs with a dosage range of 20- 40 mg daily, possibly not exceeding 60 mg but would not be practical for SSRIs like sertraline or fluvoxamine where higher dosages are used. Abrupt discontinuation of SSRI is never recommended and tapering over a period of time should always be the rule.

SNRIs in children and adolescents

Health Canada has not approved any of the serotonin/norepinephrine re-uptake inhibitors for the treatment of children and adolescents. Venlafaxine is rarely used in the treatment of children with depression as it has not shown any superiority over placebo (Mandoki, Tapia, Tapia, Sumner & Parker,1997) but may have shown some effectiveness in depressed adolescents (Emslie, Findling, Yeung, Kunz & Li, 2007). Venlafaxine (extended release XR) is sometimes prescribed off-label mostly in adolescents possibly because some studies have shown significant improvement in the treatment of childhood anxiety disorders both generalized anxiety disorder and social anxiety disorder (Ronsley et al., 2010). Since venlafaxine has a relatively short half-life about 3-13 hours (average 5 hours), more frequent and severe discontinuation reactions can be anticipated. One study reported an incidence of 78% within 3 days despite a taper of up to 2 weeks (Fava, Mulroy, Alpert et al., 1997). The most common symptoms reported in that study were dizziness or lightheadedness followed by excessive sweating, irritability, dysphoria and insomnia. Although venlafaxine's discontinuation symptoms have been reported as mostly similar to the SSRIs (Haddad et al., 2001; Fava et al., 1996), an 8 week double-blind study of 163 subjects treated with sertraline (50-150 mg/day) versus venlafaxine XR (75-225 mg/day) reported that venlafaxine was associated with a higher burden of moderate to severe discontinuation symptoms (Sir, D'Souza, Uguz, George, Vahip, Hopwood et al., 2005). Other more

serious symptoms have also been reported with venlafaxine discontinuation and include auditory and visual hallucinations, akathisia (Haddad, 2001), illusions (Louie, Lannan, Kirsch & Lewis, 1996), prolonged delusions (Koga, Kodaka, Miyata & Nakayama, 2009), tinnitus (Farah, Lauer & Thomas, 1996) as well as other isolated but significant symptoms such as palinopsia, persistent and recurrent visual images (Spindler, 2008) and a transient narcolepsy-cataplexy syndrome (Nissen, Feige, Nofzinger, Reiman, Berger et al., 2005). No reports were found on duloxetine, the other available SNRI, in children and youth possibly due to limited use. One study in adults reported discontinuation symptoms in the range of 43 % in the patient group versus 22.9 % in the placebo group following its abrupt cessation (Perahia et al., 2005). Duloxetine has a short half life of about 12 hours and a discontinuation syndrome comparable to the SSRIs and venlafaxine with a most distressing symptom being frequent and long lasting electric shocks inside the head (Pichot and Ansseau, 2008). The SNRIs have not demonstrated better effectiveness over the SSRIs (Weinman, Becker. & Koesters, 2008) but the risk of developing more frequent and significant discontinuation symptoms is higher. Discontinuing venlafaxine can be very difficult and a distressing experience for some patients. Even with an extremely slow taper they many still develop serious adverse effects while others may be unable to completely discontinue the drug (Kotzalidis, Patrizi, Koukopoulos, Savoia & Ruberto et al., 2007).

Recommendation

Physicians who prescribe SSRIs (or SNRIs) off-label to children need to be familiar with the adverse effects. To ensure better adherence to the medication prescribed they should set up frequent follow ups especially during the first few weeks of treatment and slowly adjust the frequency of visits over an adequate period of time. This will avoid undue risks related to both non-adherence and abrupt cessation of medication by either the child or the parents. Physicians need to be aware of the frequency of non-adherence. A good adherence rate on antidepressant medications has been reported as 42.5%, partial adherence at 28.7% and poor adherence at 28.8% (Judge et al., 2002). Adherence may be good for the first few weeks of initiating the medication as the youth and parent would have been informed that it will take a while to work and it must be taken daily. Unfortunately after a few weeks the youth or parents may abruptly stop the medication because of continuing side effects or what they perceive as ineffectiveness especially if there are no regular follow-ups by the treating physician. For an SSRI with a short half-life like paroxetine, often used for Social Anxiety Disorder in teens, missing just a few doses may result in real distress or further impairment in functioning. Patients and their families should be fully informed of the risk of adverse events associated with the use of antidepressants (Cheung, Emslie & Maynes, 2004). It is also crucial to inform the youth and their parents of the risks of sudden discontinuation of these medications so that they themselves establish the connection between non-adherence, cessation of medication and discontinuation symptoms. There are usually more concerns when the symptoms are unexpected leading patients to worry endlessly and making inappropriate decisions regarding their condition or the medication. They should be told of Health Canada warning about SSRIs which states:

> "Do not discontinue your medication on your own. It is very important that patients do NOT stop taking their medication without first consulting with their doctor due to the labeled risk of discontinuation symptoms with all of these drugs" (British Columbia Ministry of Health Services, 2010).

Patients should be advised that the physician makes all necessary medication adjustments. They should be warned about not making any sudden medication changes on their own without first consulting with the physician even if they feel they have recovered and no longer need the medication or they feel it is not effective. The physician also needs to be aware of the family situation and be one step ahead of possible abrupt cessation scenarios such as the child running out of medication because of financial problems, not filling out a prescription on time due to a level of family disorganization or a child whose parents are separated visits a non-residential or anti-medication parent. This parent may abruptly stop the medication during the visit causing unnecessary distress to the child. Too often parents blame "the flu" for discontinuation symptoms and physicians need to be aware that such complaints as well as complaints of ineffectiveness or worsening of symptoms on an adequate dose of an SSRI may relate to non-adherence and treatment interruptions. This is particularly common in teenagers who may be placed on an SSRI for anxiety or depression and often miss their medication for several days especially on the weekends when they do not want to mix the medication with alcohol. This is where physicians owe it to the child or youth to use their knowledge of the actual benefits versus the risks before prescribing such medication. Also parents of young children often leave the medication for the child to take without supervision and doses get missed. They then complain that the child is getting worse. Physicians should be aware of the symptoms of discontinuation and that many such complaints could be a discontinuation reaction. They should actively inquire about missed doses or unreported downward adjustments and even cessation of the medication (Warner et al, 2006). Even if these symptoms only last a day or two the concerns and phone calls from the parents can lead to unnecessary augmentation, cessation or change of medication when all that was needed was just reassurance and education to ensure better adherence and understanding of the medication. An SSRI with a very long half-life such as fluoxetine may be the medication of choice

for use in children and adolescents and would minimize the severity of an adverse discontinuation reaction. It has even been suggested that tapering may not be routinely needed with fluoxetine (Haddad, 2001). So far there have been no reports of incidences in children but tapering is still strongly advisable to avoid any discomfort to the patient.

Conclusion

This paper has reviewed some of the important aspects of the SSRI (and SNRI) discontinuation syndrome with special attention to children and adolescents. The weakness of this review is that most of the information came from the adult literature due to a lack of studies and publications in children. The lack of clear indications and approval of SSRIs for use in children and youth in Canada makes educational activities and research difficult. Many features of the discontinuation syndrome are described as similar in children, adolescents or adults including time of onset, common symptoms, duration and response to treatment (Diler et al., 2000 & 2002). Abrupt discontinuation rather than gradual tapering may be more common in children and especially adolescents for the various reasons previously mentioned. Fortunately, in the majority of cases symptoms are mild and require no active treatment although symptoms related to paroxetine and venlafaxine, used in the treatment of anxiety disorders in youths, can be fairly significant and discontinuation can be a problem. There is still a need to identify this condition early as failure to recognize discontinuation symptoms may lead the physician to think that a relapse of the treated condition is occurring and he/she may re-start treatment with the same medication instead of dealing with the discontinuation symptoms. The patient feels better once back on the SSRI. A vicious cycle thus develops as each time the physician tries to discontinue the medication the same complaints occur and medication is continued longer than necessary. The consequences of stopping the medication and fear of experiencing strong withdrawal effects can lead some patients to continue these medications longer than necessary even when they are ready to stop (Verbeek-Heida & Mathot, 2006). Most of the discontinuation symptoms are physical and misdiagnosis can also lead to unnecessary investigations to clarify the physical complaints or to inappropriate treatment (Haddad, 2001) including use of other medications. It is up to the treating physician to be vigilant and minimize the risk of the discontinuation syndrome when a child is prescribed an SSRI.

In the adult population the frequency and severity of the discontinuation syndrome is linked with the SSRI half-life. Fluoxetine has the longest half-life of the SSRIs and has been shown to have a milder discontinuation reaction than paroxetine or venlafaxine whose half-lives are shorter. This also seems to be the case in children although reports so far looking at half-lives alone between children, adolescents and adults have been confusing. Based on half-lives alone, children who have a higher drug metabolism rate than adults would be more vulnerable (Diler et al., 2002). As this does not quite seem to be the case, any difference between child, adolescent and adult in the presentation of the discontinuation syndrome may not be explained simply on the basis of half-life. Also based on half-life, the severity should be greatest with fluvoxamine (shortest half-life) but paroxetine seems to have the most severe reaction. There may be other mechanisms involved and other explanations like muscarinic receptor blockade and rebound or differences in the potency of the serotonin receptor blockade as paroxetine is a more potent muscarinic receptor antagonist and a more potent inhibitor of serotonin reuptake than other SSRIs (Bogetto et al., 2002). Further studies are required to clarify the issues regarding the discontinuation syndrome specific to children and adolescents especially prospective studies with a special focus on fluoxetine. Until then, the diagnosis and clinical features of the syndrome may continue to be based on the adult criteria. Finally, with all the apprehension regarding the use of SSRIs in children and adolescents this is an adverse reaction that is quite preventable with good clinical management. Many of the problems associated with the discontinuation syndrome arise when the symptoms are unexpected or misdiagnosed (Haddad, 2001).

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