DEPRESSION IN ADOLESCENTS — USE OF SSRIs

This Medifile aims to raise awareness of reported adverse drug events and subsequent warnings issued, among others, by the FDA and the UK Committee on Safety of Medicines (CSM). South African caregivers are encouraged to act and report any adverse events observed in day-to-day practice.

Depression affects 10% of children and adolescents worldwide. Suicide is ranked as the third most common cause of death among adolescents in developed countries. By the year 2020, depression will be the second most common cause of death worldwide. The safety and efficacy of medicines used for the treatment of depression is therefore crucial.

The prevalence of depression is increasing in the 15 - 19 - year age group. Depression is twice as common in teenage girls compared with teenage boys. A large percentage of depressed teenagers and children have co-morbid psychiatric disorders.

COMPLEXITY OF DIAGNOSING DEPRESSION IN ADOLESCENTS

Diagnosing depression in children follows the same criteria as in adults. Diagnosis is often complicated by medical conditions that may mimic a depressive episode. Investigations must be done to exclude diagnoses other than depressive disorders, e.g. hypothyroidism, substance use or exposure, and other psychiatric disorders.

RECOMMENDED TREATMENT IN ADOLESCENTS AND CHILDREN

Psychotherapy

Psychotherapy is the first step in the treatment of depression and involves cognitive behavioural therapy and interpersonal psychotherapy. It has proven to be very successful in treating mild to moderate depression in the paediatric and adolescent age group, but may be less effective in severe depression. Specialty care is sought for adolescents in whom suicidal tendencies have presented or in whom lack of response to treatment is illustrated.

Drug treatment

Drug therapy is only recommended once other measures have failed. Therapy should be individualised and treatment is dependent upon the type of depression, past history and cost of medicines. There is much debate as to what is appropriate antidepressant therapy for children and adolescents. No antidepressants are expressly registered for patients under 18 years of age. The issues relating to the 'off label' use of many of the antidepressants are addressed in this article.

Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are not recommended as treatment in adolescents owing to their side-effect profile. TCAs are cardiotoxic in overdose. They have been linked to sudden cardiac death even at therapeutic doses and therefore cardiovascular monitoring is advised. TCAs also lower the seizure threshold and their anticholinergic action produces negative effects, including confusion, tachycardia and blood pressure changes, to mention a few. There is no evidence to support the use of MAOIs in adolescents and because of dietary restrictions associated with this class of drug, it is not recommended. Selective serotonin re-uptake inhibitors (SSRIs) have not been researched extensively in adolescents and children. SSRIs are used 'off label' in the treatment of depression in the adolescent and paediatric population.

Selective noradrenaline re-uptake inhibitors (SNRIs) are also used off label and according to Wyeth, worldwide over 3 000 patients under 18 have been receiving treatment with venlafaxine in the past year (a warning has however been issued — refer 'Way forward in the study of SSRIs below).

In some cases SSRIs and the SNRIs have been successful in treating major depressive disorder (MDD) in the under-18 age group. At present there are no other treatment options available for adolescents and children.

STRONGER WARNINGS FOR SSRIs

The debate over SSRI use in the adolescent population began more that 10 years ago, when increased suicidal tendencies in patients on SSRI treatment and the sudden improvement upon withdrawal of the SSRI were reported.

Several international authority groups have issued comments recently:

- The UK's National Institute of Clinical Excellence (NICE)

has stated that SSRIs are not recommended for the initial treatment of mild depression.

- The FDA warnings regarding SSRI and SNRI use were issued after the review of clinical trials on antidepressants in the paediatric and adolescent population with MDD. It was noted that a considerable number of patients exhibited symptoms of suicidal tendencies and thoughts as well as self-harm. This information was previously not apparent as the studies had classified the behavioural changes as 'emotional lability'. This term did not necessarily imply any increased suicidal risk.

It was eventually concluded that the risks of SSRI and SNRI use outweigh the benefits. The FDA has requested manufacturers of antidepressant drugs to add warnings to their package inserts, recommending close observation of patients for worsening of depression or emergence of suicidal tendencies.

- With regard to MDD in children and adolescents, the following is advised by the CSM in the UK:
    - The risk-benefit balance is *unfavourable* for sertraline, citalopram and paroxetine.
    - Fluvoxamine is *presumed unfavourable* as it is not possible to assess the data owing to the inconsistency of trial information. The safety and efficacy in adults cannot be extrapolated to under 18s.
    - Escitalopram is *presumed unfavourable*, extrapolated from citalopram.
    - The review of venlafaxine clinical trial data has revealed that *nervous system adverse effects were significant* compared with placebo. The nervous system events included depression, depersonalisation, confusion and agitation, to mention a few.
    - Fluoxetine has *a favourable* risk-benefit balance.

According to the CSM's available data, paroxetine, sertraline, citalopram, escitalopram and venlafaxine are now contraindicated in the treatment of depression in the under-18 age group.

According to the CSM and FDA's recommendation, children and adolescents currently receiving SSRI treatment and who are responding well, should complete the usual course of treatment. If the response is inadequate, specialist advice should be sought. Discontinuation of medication may be appropriate in patients whose depression worsens and in whom suicidal behaviour and self-harm become apparent. The drug should not be stopped abruptly, but tapered off. The tapering-off period is dependent upon dose, the patient and the duration of treatment.

There are no SSRIs or SNRIs registered for use in under-18s for major depressive disorder in Canada, the UK, Ireland, New Zealand, Australia and the Netherlands. In the USA, only fluoxetine is approved for the treatment of MDD in children aged 8 years and above.

DO SSRIs INCREASE OR DECREASE SUICIDE?

There is no evidence to suggest that antidepressants prevent suicide. The suicidal rates for patients taking TCAs are 0.4%, placebo is 0.2% and fluoxetine 0.3%. There is no clear correlation between increased prescribing of antidepressants and the fall in suicide rates.

A common feature of psychiatric disorders is the risk of suicidal tendencies. Similar cases have been found where increased suicidal tendencies have occurred in all classes of antidepressants.

The Task Force report of the American College of Neuropsychopharmacology suggests two possible explanations for the increased rate of suicidal tendencies and self-harm in those using SSRIs.

- SSRIs fail to relieve suicidal behaviour that is part of depression.
- SSRIs trigger a novel set of suicidal emotions and behaviours. This includes a mixed mood state of mania and depression, which in turn carries a greater risk of suicidal behaviour.

EFFECTS OF SSRIs IN NEONATES

Withdrawal effects in newborn babies have been documented. Pregnant women receiving SSRIs have given birth to babies in whom adverse effects such as hypotonia, agitation, convulsions, tremor and respiratory disorders have been noted. The withdrawal effects of paroxetine in adults is quite pronounced compared with other SSRIs, and the same seems to be true for neonates. The withdrawal effects are attributed to *in utero* exposure during the third trimester.

SSRI withdrawal effects have also been experienced in neonates as a result of breast milk transfer. Nine reports have been cited with sertraline, 2 with paroxetine and 2 with fluoxetine. Fluoxetine and citalopram have a much higher transfer rate compared with paroxetine.

It has been recommended that infant formula be used in these situations and that SSRIs should not be prescribed to sexually active girls not using contraceptives.

REGISTRATION IN SOUTH AFRICA

There are currently no SSRIs or SNRIs registered for the treatment of MDD in children and adolescents in South Africa. The indications for these drugs are as follows:

- **Fluoxetine**
  - Indicated for depressive disorders, bulimia nervosa and obsessive compulsive disorder (OCD). Also used off label for anxiety.
  - Not registered for use in adolescents and children.
  - Category C in pregnancy; increased risk of premature birth.
  - Not recommended during lactation as the infant receives 10% of the maternal dose.
  - Trade names include Prozac, Lorien, Nuzak, ProHexal, Sandoz Fluoxetine and Sanzur.
- **Paroxetine**
  - Indicated for MDD, especially where sedation is undesirable, panic disorder, OCD and social phobia.
  - Not recommended for use in under-18s.
  - Safety has not been established in pregnancy.
  - Excreted in breast milk.
  - Trade names include Aropax.
- **Citalopram**
  - Indicated for depression.
  - Not indicated for use in under-18s
  - Safety in pregnancy not established.
  - Trade names include Cipramil, Cilift and Talomil.
- **Fluvoxamine**
  - Indicated for depression.
  - Not indicated for use in under-18s.
  - Safety has not been established in pregnancy.
  - Trade names include Luvox.
- **Sertraline**
  - Indicated for depression.
  - Not indicated for use in under-18s.
  - Safety has not been established in pregnancy.
  - Trade names include Zoloft and Serlife.
- **Venlafaxine**
  - Indicated for the treatment of major depression.
  - Not registered for use in under-18s.
  - Safety not established in pregnancy.
  - Trade names include Efexor and Efexor XR.
- **Escitalopram**
  - Indicated for the treatment of depression and panic disorders.
  - Not registered for use in under-18s.
  - Safety has not been established in pregnancy.
  - Trade names include Cipralex.

DRUG COMPANY WARNINGS

Solvay Pharma, Pfizer, GlaxoSmithKline, Wyeth and Lilly, manufacturers of ethical drug products, have all incorporated additional precautions in their product monographs, warning against emotional and behavioural changes experienced in under-18s on treatment. The changes to be wary of include akathisia, agitation, disinhibition, emotional lability, hostility, aggression and depersonalisation. In certain cases, onset of events presents within a few weeks of initiating treatment.

CLINICAL TRIAL EVIDENCE POOR

For ethical restrictions, clinical trial results for the treatment of depression in adolescents and children are poor. The available trials were conducted over 10 weeks or less, whereas the mean duration of treatment in clinical practice is 6 months and longer. It is known that during the early phases of treatment, suicidal thoughts and behaviour increase owing to increased levels of serotonin and noradrenalin post-synaptically. The main problem is the lack of accurate and meaningful psychopharmacological research in adolescents and children.

Drug level monitoring is unlikely to be helpful as a method of predicting adverse effects, as there is a huge inter-patient variability both in the response to and the metabolism of SSRIs. Due to the poor quality of basic research design, the risk profile was overlooked. Another problem is the difficulty in obtaining clinical trial information from drug companies as they are not compelled to release this information. Clinical trial information is only available if the drug company is pursuing a product licence for a specific indication in a specific age group.

Psychiatrists are therefore questioning the SSRI warnings, as the validity of the internal and external trials undertaken has raised key issues:

- The symptoms reported during the clinical trials are part of an 'activation syndrome' with SSRIs that has been a common observation in literature for years.
- It is still debatable whether these symptoms indicate increased self-harm.
- This new CSM recommendation is based upon a small number of unsatisfactory studies in the paediatric and adolescent age group. The SSRI warning may be overestimated.
- The rate of suicidal behaviour and tendencies among adolescents and children on SSRIs is not statistically different from that in youth on placebo in some studies.

WAY FORWARD IN THE STUDY OF SSRIs

Rigorous monitoring of behavioural and emotional changes should be recommended in all patients taking antidepressants, irrespective of age. This dilemma regarding SSRIs reinforces the importance of continuously evaluating the benefit-risk balance for all medicines. Paediatric safety and efficacy cannot be extrapolated from trials performed in adults.

NICE will publish treatment guidelines for the management of depression in the adolescent and paediatric population within a year. A document termed 'Pharmacovigilence' will soon be available to facilitate drug monitoring in countries where it is currently unavailable.

In the interim, the FDA plans to work closely with drug companies to optimise safe drug usage, and implement proposed labelling changes and other safety information.

There are currently no guidelines available for the treatment of MDD in adolescents and children in South Africa. No official warnings have been issued in South Africa regarding SSRIs in the under-18 population group. Wyeth has, however, issued a statement that venlafaxine (Efexor) should not be used in patients under 18 years of age.

The treatment of depression in children and adolescents is a challenge and more investigation is required to address all issues effectively.

The purpose of this article is to raise awareness and encourage caregivers to report any adverse effects observed. In South Africa adverse drug reactions should be reported in writing and addressed to: National Adverse Drug Event Monitoring Centre, c/o Department of Pharmacology, Faculty of Health Sciences, University of Cape Town, Observatory, 7925 or faxed to the centre at (021) 448-0503.

References available on request.

Please feel free to use the following e-mail address should you have any questions or comments or suggestions for future articles:

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