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The treatment of major depression with fluoxetine

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Abstract

Depression is a common mental health disorder that affects at least 350 million people worldwide and exerts a negative effect upon a person's physical, mental and social functions, and it is associated with an increased risk of premature death. The treatment of depression involves the use of antidepressants and selective serotonin inhibitors are currently the first line of treatment. In particular, fluoxetine is safe and effective in the treatment the disorder. It is one of the few antidepressants licensed for use in children under the age of 18 years in the UK. Fluoxetine is associated with fewer dose adjustments compared to other SSRIs and this simplifies therapy and may improve outcomes. However, fluoxetine induces a number of side effects like, nausea, insomnia, sexual dysfunction and its interaction with monoamine oxidase inhibitors can cause the serotonin syndrome.

Introduction

According to the World Health Organisation (WHO) report, major depression affects at least 350 million people worldwide ranking third on the list of global burden of disease (WHO 2008). It can occur at any age and its incidence is twice higher among women than men (Sclar *et al.* 2012). Sufferers and their families bear substantial individual, economic and social costs because the illness wields a negative effect upon the patient's physical, mental and social functions. In fact, depression produces the greatest decline in health compared to long term physical conditions like angina, arthritis, asthma, and diabetes (Moussavi *et al.* 2007). From an economic perspective, the total annual cost of major depression was estimated to be 118 billion euros in Europe in 2004 alone, accounting for 33% of the total

healthcare cost (Sobocki *et al.* 2006). These personal, social, familial and economic costs are a direct result of the symptoms of depression.

The symptomatology of depression

The symptoms of major depression can include low mood, impaired concentration, increased or decreased sleep, altered appetite or weight, psychomotor disturbance, fatigue, muscle tension and pain, social withdrawal, loss of interest in usual activities, crying, weeping feelings of guilt, worthlessness, suicidal ideation or behaviour(Thomas and Chan 2012). For the diagnosis of major depression, the symptoms of low mood and/or loss of interest should be present continuously in addition to four other symptoms for a period of 2 weeks or more (American Psychiatric Association 2013).

Putative mechanism of depression

Despite the well-defined symptomatology, major depression appears to be heterogeneous mental health disorder whose pathophysiology is currently unclear (Rahe *et al.* 2014). Environmental and personal biological vulnerabilities appear to play a significant part but precisely how these factors interact is not firmly established (Dichter *et al.* 2014) and this has given rise to several theories of depression. However, the theory that has direct relevance to current antidepressant treatment is the monoamine hypothesis. This theory simply suggests that depression is due to a reduction in concentration of monoamine neurotransmitters at the synapse in specific regions of the brain. These neurotransmitters are serotonin, noradrenaline and dopamine. The treatment of depression with antidepressants aims to reverse this monoamine neurotransmitter. The restoration of monoamines to normal levels corresponds with mood alleviation and this is the key function of antidepressants.

Fluoxetine and the treatment of depression

The use of antidepressants started in the 1952 with iproniazid, a monoamine-oxidase inhibitor and later in 1955 with imipramine, a tricyclic antidepressant. However, the poor tolerability and toxicity of these drugs stimulated the search for other drugs with a better tolerability and safety profile. This led to the discovery of the Selective Serotonin Reuptake Inhibitors (SSRIs) and these drugs have become the

most widely used groups of antidepressants (Hetrick *et al.* 2007). SSRI drugs operate mainly by selectively inhibiting the reuptake of serotonin in the synaptic cleft. As a class, they are ostensibly effective, safe in overdose and have a reduced side effect burden.

Fluoxetine was one of the first SSRI to be marketed in 1987 and demonstrates an effectiveness that is at least equal to that of imipramine and other tricyclics (Pary *et al.* 1989). A review of 87 different randomised controlled trials with a total of 9087 patients, concluded that fluoxetine is safe and effective in the treatment of depression and has advantages over first generation antidepressants in terms of safety (Rossi *et al.* 2004). These early findings are supported by a relatively recent Cochrane systematic review of 171 randomised controlled studies that found fluoxetine to be as efficacious and better tolerated compared to tricyclic antidepressants (Magni *et al.* 2013). In addition to the treatment of depression, some SSRIs and fluoxetine in particular are used for the treatment of obsessive compulsive disorder, panic disorder, bulimia nervosa.

Fluoxetine is well absorbed after oral administration, with peak plasma concentrations observed after 6 to 8 hours and has an elimination half-life of 1 to 4 days. It has an active metabolite, norfluoxetine which has an elimination half-life of 7 to 10 days(AMA 1992). This extended half-life appears to protect against intermittent non-adherence and the occurrence of the serotonin discontinuation syndrome. Fluoxetine is associated with fewer dose adjustments compared to other SSRI and this simplifies therapy and may improve outcomes (Stokes and Holtz 1997).

In the treatment of adults with major depression, a dose of 20 mg/day is recommended. If necessary, the dosage can be reviewed and adjusted within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate (Stokes and Holtz 1997). For those who show insufficient response to the 20mg dose, the dose can be increased to higher doses up to a maximum of 60mg/day (EMC Medicines 2015; Stokes and Holtz 1997). However, dose escalation may increase the potential for adverse side effects in some patients and therefore, dose adjustments should be made carefully on an individual patient basis with view to maintain the patient at the lowest effective dose. Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from

symptoms (NICE, 2009). With respect to the older persons, fluoxetine is well tolerated and effective in treating depression but caution is recommended when increasing the dose (Stokes and Holtz 1997). The daily dose should generally not exceed 40mg though maximum recommended dose is 60mg/day (EMC Medicines 2015). Fluoxetine is also widely used in the treatment of depression in children and adolescents.

The treatment of children and adolescents with antidepressants has evoked lively debates about their safety in this population (Gibbons *et al.* 2007). There is black box warning against their use in children and adolescents because of their purported tendency to induce suicidal ideation and behaviour in this population according to at least one meta-analytic review (Sparks and Duncan 2013) although, at least one meta-analysis challenge this view (Gibbons *et al.* 2012). In spite of this dissent, the bulk of evidence in the extant literature suggest a link between suicidal ideation and the use of SSRIs in children and adolescents (Sparks and Duncan 2013). The situation is further complicated by the consistent finding from literature reviews examining the risks and benefits of SSRIs which consistently highlight the potentially serious consequences of untreated depression in children and adolescents (Eapen and Crncec 2012). On balance, these arguments seem to support SSRIs are an effective treatment option in children and adolescents with depression in clearly defined clinical situations (Hetrick *et al.* 2007). In this regard, NICE guidelines advise starting SSRIs in this population only in combination with a specific psychological treatment, and only if there has been no response to psychological treatment over four to six weeks. Close supervision of children and adolescents on SSRIs is necessary especially during the early stages of treatment stages and following dose changes (NICE 2015).

Several SSRIs including citalopram and sertraline have been used in the treatment of depression in children and adolescents but according to a Cochrane review, fluoxetine is the only SSRI where there is consistent evidence from trials showing that it is effective in reducing symptoms of depression in both children and adolescents (Hetrick *et al.* 2007). Further, fluoxetine is the only antidepressant with marketing authorisation for use in children and young people aged between 8 and 18 years (NICE 2015).

Treatment should be initiated and monitored under specialist supervision (NICE 2015). The starting dose is usually 10mg/day and dose adjustments should be made carefully, on an individual basis to maintain the patient at the lowest effective dose. After one to two weeks, the dose may be increased to 20mg/day and treatment can be continued for up to 9 weeks (EMC Medicines 2015; NICE 2015). Children with lower weight are likely to present with higher plasma levels; therefore therapeutic effect may be achieved with lower doses. For children who respond to treatment, the need for continued treatment after 6 months should be reviewed. If no clinical benefit is achieved within 9 weeks, treatment should be reviewed (EMC Medicines 2015).

Fluoxetine induces a number of side effects including sexual dysfunction, insomnia, headache, diarrhoea and nausea. Its interaction with monoamine oxidase inhibitor (MAOI) can cause a fatal reaction, the serotonin syndrome. Therefore, treatment with fluoxetine should only be started 2 weeks after discontinuation of an irreversible MAOI (NICE 2009). Because fluoxetine is extensively metabolized by the liver and excreted by the kidneys, a lower dose is recommended in patients with significant hepatic dysfunction. Abrupt discontinuation of fluoxetine should be avoided and the dose should be gradually reduced over a period of at least four weeks in order to reduce the risk of withdrawal reactions(NICE,2009).

Conclusion

The prevalence and consequences of depression are clear and several treatments for the illness are available but the use of antidepressants remains central. SSRI in particular are used as the first line of treatment. Fluoxetine, one of the first SSRIs to be marketed has a relatively safe profile and is effective in the treatment of depression. In particular, fluoxetine has market authorisation for use in children between the ages of 8 and 18years old. However, fluoxetine induces a number of side effects and its interaction with MAOIs can cause the serotonin syndrome.

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