Paroxetine for the treatment of depression in children and adolescents: A suicidal choice?

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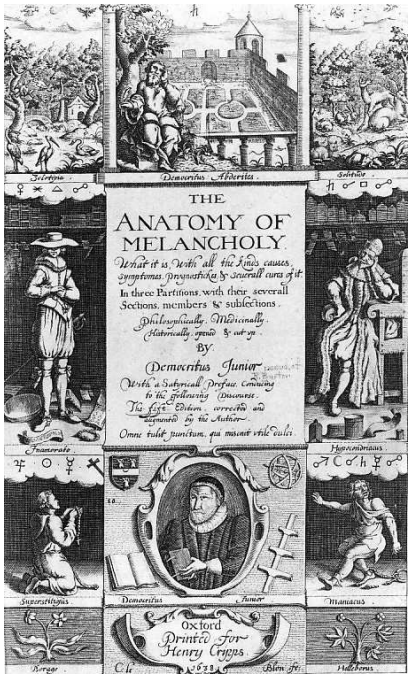

Frontispiece from the1638 edition of Robert Burton's *The Anatomy of Melancholy*, Wikimedia Commons

Introduction

Although major depression is usually associated with adults, research has shown that a substantial proportion of children and adolescents are also affected. Before the 1970s, children and adolescents were thought to be incapable of developing depression due to immaturity and less life experience. However, research over the past thirty years shows that children are indeed capable of experiencing depressive states, although with a variety of different symptoms to those seen in an adult experiencing major depression. These include the following:

- Low self esteem
- Attention to negative aspects of situations
- Feelings of hopelessness
- General negative feelings (Coghill & Usala, 2006)

Suicide is the third leading cause of death in adolescents. Recently, studies surrounding antidepressants, particularly paroxetine have focused upon the side effects when prescribed to adolescents, in particular an increased risk of suicide.

Amine Neurotransmitters and Depression

Surprisingly, little is known about the exact causes and mechanisms of the illness but it is generally considered to involve the disruption of a group of neurotransmitters referred to as the amines, which includes dopamine, noradrenaline and 5–hydroxytryptamine otherwise known as serotonin. Serotonin is present in a relatively small number of neurones in specific areas of the brain. It is generally

excitatory and is involved in the regulation of mood, sleep, temperature and locomotion. It is formed by enzymatic action from the dietary amino acid tryptophan.

Figure 2. Paroxetine (GlaxoSmithKline) By Tokino GFDL(GNU Free Documentation License) Wikimedia

In the brain the cells containing serotonin are concentrated in the brainstem and the axons project forward into other areas of the brain and also down to the spinal cord, where they affect movement. The strongest evidence that serotonin neurones are involved in depression is the action of selective serotonin reuptake inhibitors (SSRI's), as they are one of the most clinically effective and commonly used treatments (Sahgal, 1993). There is however, a lack of evidence that patients with depression actually have lower levels of both serotonin and noradrenaline in the brain. One of these SSRI's, called paroxetine, has been linked with suicide in childhood depression.

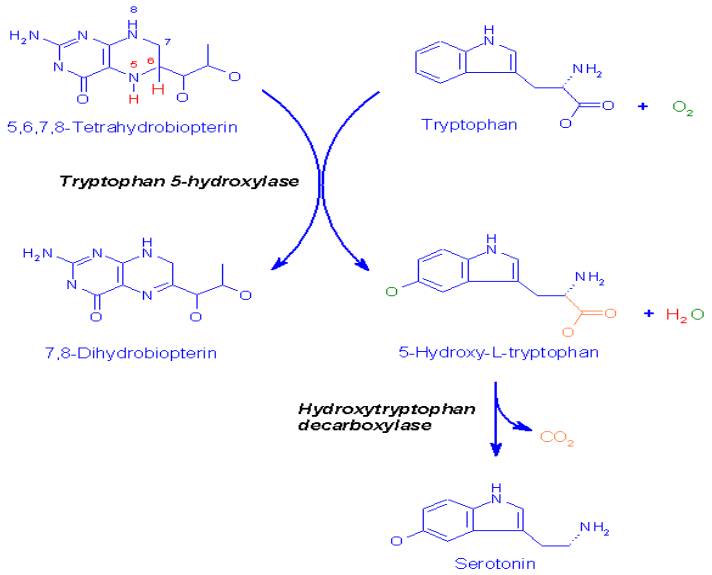

Figure 1. The synthesis pathway of serotonin. The amino acid precursor tryptophan is converted to 5-HTP by tryptophan 5-hydroxylase and then to serotonin by hydroxytryptophan decarboxylase. Figure taken from (King, 2007).

SSRI and Paroxetine Pharmacology

Selective serotonin reuptake inhibitors (SSRI's) counteract a lack of serotonin within certain parts of the brain by preventing the re-uptake of the neurotransmitter in the synapse. Thus the action of naturally released serotonin is prolonged. Many of these drugs have been successful in treating depression but all have side effects such as nausea, sleep disturbance and weight gain, although these are generally less severe than has been reported in other groups of antidepressants (Wolpert, 2001).

Paroxetine is one of the more potent of the SSRI's and is involved in the treatment of various mental illnesses including depression, obsessive compulsive disorder and panic disorders. The affinity of paroxetine for serotonin receptors is approximately 2-3 times higher than that of serotonin itself and it works in the same way as other SSRI's, ultimately resulting in a higher concentration of serotonin in the synaptic cleft. Long-term administration of paroxetine results in secondary adaptive receptor changes through a decrease in the responsiveness of serotonin receptors, leading to greater serotonin release with each action potential (Wu et al., 2007).

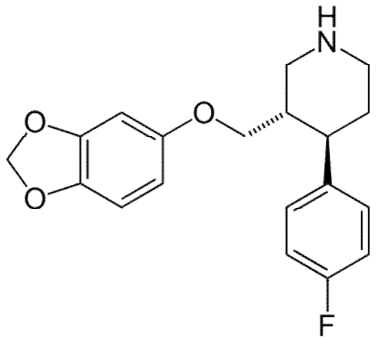

Figure 3. 2D chemical structure of paroxetine

Childhood Depression and Treatment with SSRI's

There are problems associated with diagnosing childhood depression, as children often have difficulty expressing their feelings and parents and other caregivers are required to supply the majority of the information. This is coupled with the usual stigma surrounding depression and thus makes it difficult to diagnose. In terms of the psychological perspective of depression, studies have shown that family environment, major life events and the general temperament of the child all have an effect on their susceptibility to depression (Malhotra & Pratim Das, 2005).

On the other hand, the biological evidence includes significant anatomical changes in areas of the brain, which correlate with findings in adult studies. Steingard et al. (1996) showed that children who had been diagnosed with depression showed an increase in the ratio of lateral ventricular volumes to total cerebral volume, and smaller ratio of frontal lobe volume to total cerebral volume. Other studies show similar morphological changes in certain structures within the brain.

The most common antidepressants prescribed to children are fluoxetine, citalopram and sertraline as these are deemed the safest, although studies generally show that responses to a placebo are a lot higher in children than in adults (Wagner, 2005). There is however limited data on the subject as recognition is often difficult and depression is often associated more with adults (Cheung et al., 2005).

Interestingly, the older tricyclic antidepressants are generally found to be less effective in children and adolescents than adults, and so SSRI's are the favoured course of antidepressant treatment. This has provided a route for research into the development of the serotonin and noradrenaline systems, as they may provide an explanation for this difference and could be an important factor in producing new drugs (Murin et al., 2007).

Paroxetine treatment and suicide in children and adolescents

In June 2003 the Medicines and Healthcare products Regulatory Agency (MHRA) for Great Britain, received data for all trials related to paroxetine from the drug company GlaxoSmithKline. Subsequently they issued a statement advising that paroxetine should not be used to treat patients under the age of 18 because it was ineffective and could cause increased suicidal behaviour (Cheung et al., 2005). They found that studies on children prescribed paroxetine indicated that they were between 1.5 and 3.2 times more likely to exhibit signs of suicidal behaviour than children receiving a placebo (Kondro & Sibbald, 2004).

The FDA released a similar statement and concluded that paroxetine had no more positive effects than a placebo drug. Studies also showed that suicidal thoughts and self harming behaviour were more common in patients who were prescribed paroxetine (Wooltorton, 2003).

It was also revealed that in 1998 an internal document had been released to staff at GlaxoSmithKline, telling them to withhold information regarding a number of clinical trials in order to "minimise any potential negative commercial impact". These trials revealed that paroxetine had no beneficial effect in treating adolescents with depression. The UK has since banned paroxetine from being prescribed to patients under the age of eighteen, but it should be noted that paroxetine has never actually been licensed for children but in the UK doctors can prescribe it to adolescents if the situation is deemed appropriate i.e. severe depression (Waechter, 2003).

This information greatly affected the use of paroxetine throughout the UK and the graph shown in figure 4 displays the number of prescriptions given out for different antidepressants over four years. It is clear from the graph that the number of prescriptions for paroxetine dropped significantly after mid 2002, whereas prescriptions for the other SSRI's continued to increase.

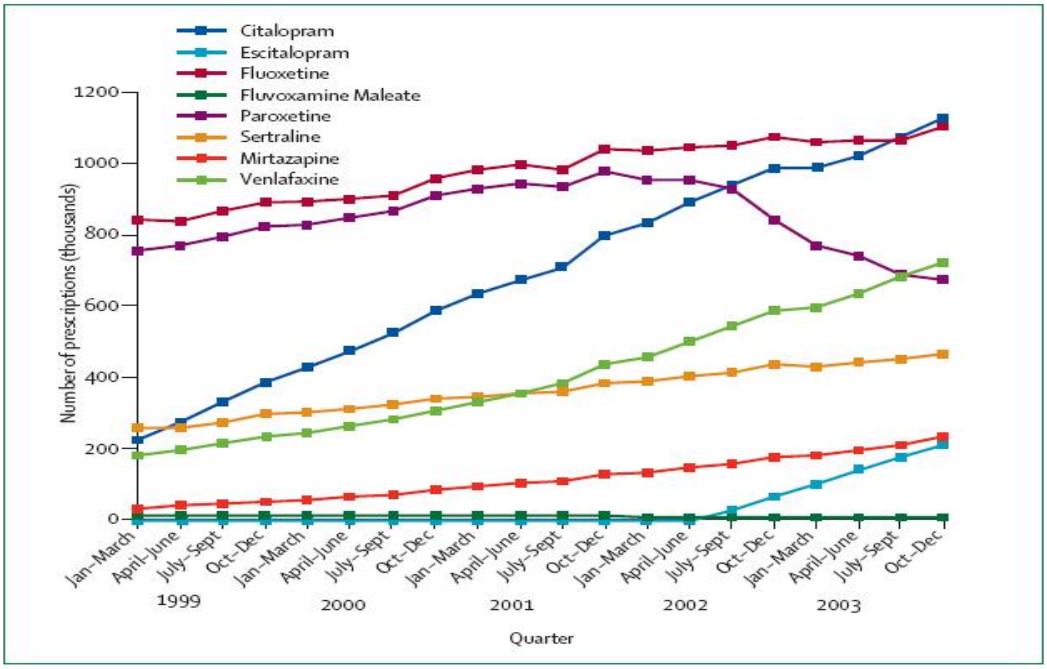

Figure 4. Number of prescriptions for different antidepressants from 1999-2003 (Ebmeier et al., 2006).

In 2005, Cheung et al conducted a review of the safety and efficacy of antidepressants prescribed to adolescents and children and included both published and unpublished data on randomised controlled trials. These included patients under the age of 19 suffering from major depression in all trials covered in the FDA safety report and any unpublished trials up to 2004. The studies included focussed on the newer antidepressants and so excluded older drugs such as tricyclics. The safety issues that were taken into account were:

- Physical side effects
- Discontinuation rates
- Suicide related events
- Rates of hostility/behavioural activation
- Method of elicitation of side effects
- Rates of mania
- Reporting of adverse effects and serious adverse effects

The review included 3 double blind placebo controlled studies of paroxetine, including one published report. Assessment was carried out in the usual way for antidepressants, which is to assess the severity of depression using the Hamilton Rating Scale for Depression (HRSD) and efficacy is defined as at least a 50% reduction from the baseline (Wu et al, 2007). The review found that all studies reported adverse effects although not all data on side effects was available due to the unpublished studies used.

One of the most recent reviews by Barbui et al., in 2008, also considered randomized placebo-controlled trials and used both published and unpublished studies. All trials assessed the efficacy of paroxetine compared to a placebo, with the first primary outcome measure being the amount of patients who discontinued treatment for any reason. Forty trials were included in the meta-analysis. The study concludes that although paroxetine is no more effective than a placebo in terms of discontinuation of use, it has a significantly greater effect on treating the depression itself. Whether it is linked to suicide remains debatable (Barbui et al., 2008).

Complications and Controversy

The controversy surrounding paroxetine and its use for children has led to a substantial drop in prescription rates which is not necessarily based on enough evidence to confirm that paroxetine is in fact linked to suicide. The recent media attention and negative press it has received have also contributed to this and it may even contribute to the worsening of suicidal ideas and behaviours in patients who are particularly vulnerable and suffer from major depression (Barbui et al, 2008).

An interesting finding from the studies is that paroxetine is often found to be no more effective than a placebo. This could mean that patients who experience no beneficial effects from the drug could therefore experience worsened symtpoms of depression and thus more suicidal behaviour. This leads to the conclusion that it is not the drug itself causing the increased suicidal behaviour but the fact that the drug is not alleviating the symptoms.

The initial difficulty of diagnosing depression in children and adolescents is also a major problem as are problems with non-compliance throughout studies. The most common way to assess depression is the use of rating scales such as the HRSD, which quite often rely on reports by patients or in the case of children, parents or

family. This is not always a reliable way of collecting data and could pose a significant problem when assessing results, particularly on the severity of the depression itself. This leads to the need for more substantial research into the exact biological mechanisms of depression, as clinical measurements of depression severity could provide more accurate data.

Similarly, there is a need for more detailed documentation and clearer guidelines on reporting the exact nature of side effects experienced when taking paroxetine and other antidepressants, as there is often great variability between studies. For example, suicide is sometimes only considered if completed, which is excluding the importance of increased suicidal "behaviours".

Future implications

The need for further research is vital in this subject area as there is surprisingly little known about an illness that is so common. The development of drug treatments that focus on serotonin receptor subtypes and the serotonin transporter molecule are promising for the future. There has also been research focussing on the production of triple monoamine uptake blockers i.e. those that inhibit the uptake of serotonin, noradrenaline and dopamine within the brain (Schechter et al., 2005) and also drugs that target GABA and peptide hormones.

The need for longer-term studies as described earlier would provide vital information on the link between antidepressants and suicide and would increase the validity and availability of studies in this area.

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Author profile

Laura is 22 years old, studied in the School of Biosciences at the University of Nottingham graduating in 2008 with a 2:2 BSc. (Hons) in Applied Biology. Laura was particularly interested in neurophysiology and is beginning her training as a clinical physiologist in this area.