PROPOSAL FOR THE INCLUSION OF FLUOXETINE (AS A REPRESENTATIVE OF THE SELECTIVE-SEROTONIN REUPTAKE INHIBITORS' CLASS), IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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Synopsis

Fluoxetine is proposed for the acute and maintenance treatment of adult individuals with moderate to severe major depression. Fluoxetine is intended as an example of the therapeutic group of the selective serotonin-reuptake inhibitors (SSRIs). There is robust evidence suggesting that SSRIs are as effective as tricyclic antidepressants and are less likely to be discontinued because of side effects.

Some differences between individual SSRIs have been highlighted, for example a difference between sertraline and fluoxetine in terms of efficacy, favouring the former, a lower propensity for fluoxetine and citalopram to cause discontinuation/withdrawal symptoms, a higher propensity for fluoxetine to cause drug interactions. However, the clinical significance of these differences is still uncertain and, currently, there is no strong scientific reason for preferring one specific SSRI over another. Therefore, one SSRI available in a generic form would be a reasonable choice from an evidence-based perspective.

1. Summary statement of the proposal

Fluoxetine is proposed for the inclusion in the World Health Organisation (WHO) Model List of Essential Medicines for the acute and maintenance treatment of adult individuals with moderate to severe major depression. Fluoxetine is intended as an example of the therapeutic group of the selective serotonin-reuptake inhibitors (SSRIs).

2. Name of the organization(s) consulted and/or supporting the application

WHO Collaborating Centre for Research and Training in Mental Health, Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Policlinico "G.B. Rossi", Piazzale Scuro 10, 37134 Verona, Italy.

3. International Nonproprietary Name (INN, generic name) of the medicine

Fluoxetine hydrochloride

4. Formulation proposed for inclusion

20 mg tablets

5. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested on the WHO Model List of Essential Medicines as an example of the therapeutic group of the SSRIs.

6. Epidemiological information on disease burden

Depression is a condition characterised by discrete episodes of depressed mood. Each episode is characterised by persistent low mood, loss of interest or pleasure in almost all activities, substantial unintentional weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, diminished ability to think or concentrate and recurrent thoughts of death. Depressive symptoms often markedly impair everyday functioning. The term major depression identifies a clinical condition characterised by at least one episode of depressed mood. The term unipolar depression is sometimes used to make a distinction between depressive episodes in the course of

major (or unipolar) depression and depressive episodes in the course of bipolar disorder (bipolar depression).

Depression can be grouped into mild, moderate and severe. Mild to moderate depression is characterised by depressive symptoms and some functional impairment; severe depression is characterised by depressive symptoms, functional impairment, agitation or psychomotor retardation, and marked somatic complaints.

Depression can affect individuals at any stage of the life span, although the incidence is highest in the middle ages. Depression is more common in women than in men. Global Burden of Disease (GBD) 2000 estimates the point prevalence of unipolar depressive episodes to be 1.9% for men and 3.2% for women, and that 5.8% of men and 9.5% of women will experience a depressive episode in a 12-month period (Murray and Lopez, 1996). These prevalence figures vary across populations and may be higher in some populations. GBD 2000 analysis also shows that unipolar depressive disorders place an enormous burden on society and are ranked as the fourth leading cause of burden among all diseases (Murray and Lopez, 1996).

Depression is essentially an episodic recurring disorder, each episode lasting usually from a few months to a few years, with a normal period in between. In about 20% of cases, however, depression follows a chronic course with no remission, especially when adequate treatment is not available. The recurrence rate for those who recover from the first episode is around 35% within 2 years and about 60% at 12 years. The recurrence rate is higher in those who are more than 45 years of age. One of the particularly tragic outcomes of a depressive disorder is suicide. Around 15-20% of depressive patients end their lives by committing suicide. Suicide remains one of the common and avoidable outcomes of depression.

7. Assessment of current use and target population

While in mild depression psychological support and watchful waiting are considered first-line interventions, in moderate to severe depression antidepressant (AD) prescribing is generally recommended (National Collaborating Centre for Mental Health, 2004). Significant improvement is seen in 70% of patients, although up to 30% of patients are placebo responders.

For decades the tricyclic ADs, considered the first-line pharmacological treatment of moderate to severe depression, have been widely prescribed by primary and secondary care physicians. In the late 1980s, however, the introduction of fluoxetine, the first of a group of AD agents known as selective

serotonin reuptake inhibitors (SSRIs), profoundly changed the epidemiology of AD drug use in primary and secondary care. Soon after their availability fluoxetine and the SSRIs acquired great popularity and in a few years became the most prescribed antidepressants in primary and secondary care; conversely, the use of tricyclic ADs gradually declined.

Currently, most treatment guidelines recommend a generic SSRI in the first-line pharmacological treatment of moderate to severe depression (National Collaborating Centre for Mental Health, 2004). This recommendation is based on randomised evidence suggesting that SSRIs are as effective as tricyclic ADs and are less likely to be discontinued because of side effects. Additionally, tricyclic ADs are more dangerous than SSRIs in overdose.

8. Treatment details

8.1 Indications for use

Acute and maintenance treatment of adult individuals with moderate to severe major depression.

8.2 Dosage regimens

Fluoxetine initial dosage is 20 mg orally a day, usually given in the morning, because insomnia is a potential adverse effect of the drug. To minimise early side effects of anxiety and restlessness, fluoxetine may be started at doses of 5 to 10 mg a day. Fluoxetine should be taken with food to minimise possible nausea. The long half-life causes the drug to accumulate in the body over a period of two to three weeks. As with all available ADs the antidepressant effect may be seen in the first three weeks, but it is much more reasonable to wait to evaluate the antidepressant activity until the patient has been taking the drug for four to six weeks. Several studies have suggested that 20 mg a day is as effective as higher dosages. The maximum daily dosage recommended is 80 mg a day. Patients are usually maintained with 20 mg a day for three-four weeks. If no signs of clinical improvements are observed, an increase to 20 mg two times a day may be warranted. The second dose is usually given at noon to avoid problems with insomnia.

8.3 Duration of therapy

Once symptoms are relieved, fluoxetine should be continued for at least 9-12 months to prevent relapse. The same dose as used for acute treatment should be prescribed. There is very limited evidence that lower doses are effective. Patients at high risk of relapse (e.g. those with 2 or more previous episodes, or those with major depression lasting more than 2 years) must continue pharmacotherapy for at least 2 years.

Although ADs are not associated with tolerance and craving, as experienced when withdrawing from addictive substances such as opiates or alcohol, some patients experience symptoms when stopping ADs or reducing the dose. These can include dizziness, nausea, paraesthesia, anxiety and headaches and, in this guideline, are referred to as discontinuation/withdrawal symptoms. Fluoxetine, due to its long half-life, is less likely than other SSRIs to cause discontinuation symptoms.

8.4 Reference to existing WHO and other clinical guidelines

In the UK, the National Institute for Clinical Excellence (NICE) issued in 2004 recommendations for the identification, treatment and management of depression for adults aged 18 years and over, in primary and secondary care. The guideline includes good practice points and evidence-based recommendations for the psychological, pharmacological, service-level and self-help interventions appropriate to each section. A generic SSRI is recommended in the first-line pharmacological treatment of moderate to severe depression (www.nice.org.uk/CG023NICEguideline).

In 2001, guidelines developed by the Canadian Network for Mood and Anxiety Treatments (CANMAT) in collaboration with the Canadian Psychiatric Association (CPA) recommended one of the SSRIs as first-line treatment of major depression (http://www.cpa-apc.org/Publications/Position_Papers/Position_Papers.asp)

The American Psychiatric Association (APA) Practice Guidelines, issued in 2000 and updated in 2005, indicated that the initial selection of an antidepressant medication should be based on the anticipated side effects, the safety or tolerability of these side effects for individual patients, patient preference, quantity and quality of clinical trial data regarding the medication, and its cost. On the basis of these

considerations, the following medications are considered optimal for most patients: SSRIs, desipramine, nortriptyline, bupropion, and venlafaxine (www.psych.org/psych_pract/treatg/pg/prac_guide.cfm).

8.5 Need for special diagnostic or treatment facilities and skills

There is no need for special diagnostic facility per se, but clinical skills in the recognition of major depression and in its categorisation into mild, moderate or severe, is required.

Although population-level screening campaigns have a negative ratio of costs to benefits, increasing the ability of primary care physicians in recognising depression in primary care patients remains a relevant factor at an individual-level of care (Gilbody *et al.* 2006; Bower and Gilbody, 2005). During everyday clinical practice, primary care physicians need to take into careful consideration any previous history of depression, unexplained physical symptoms, physical illness and disability, other medical conditions such as Cushing's syndrome, therapeutic use of corticosteroids, pregnancy or recent delivery, premenstrual syndrome or menopause, as well as recent significant life events, including birth, death, marriage, divorce, moving house, collapse of a business, redundancy, inability to find a job. Any recent changes in patient moods, such as feeling down, depressed or hopeless, should be recognised, highlighting typical diurnal variation in symptoms (patients usually report to feel a bit better in the evening than in the morning). Depressed patients lack energy, motivation and appetite, as well as interest in work and social life. Depressive symptoms are often associated with anxiety, eating disorders, obsessive-compulsive disorder, panic disorder, chronic fatigue syndrome and other psychiatric comorbidities. Primary care physicians should inquire about drug and alcohol use and abuse. Disorders of the content of thought (delusions and hallucinations) are uncommon but should be similarly investigated, given that occur in a minority of cases (psychotic depression). Patients should be asked about feeling of worthlessness and guilt, as well as about thoughts of suicide.

Primary care physicians should consider whether depression is mild, moderate or severe. This patient categorisation helps develop appropriate management and therapeutic strategies (National Collaborating Centre for Mental Health, 2004; Cipriani *et al.* 2005a).

9. Summary of comparative effectiveness in a variety of clinical settings

9.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Systematic reviews and clinical trials were identified by searching the Cochrane Database of Systematic Reviews and the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR) and the Cochrane Central Register of Controlled Trials (CENTRAL). The following terms were used: antidepressant or FLUOXETIN* OR adofen or docutrix or erocap or fluctin or fluctine or fluoxeren or fontex or ladose or lorien or lovan or mutan or prozac or prozyn or reneuron or sanzur or saurat or zactin. Medline (1966-2006) and Embase (1974-2006) were searched using the search term "fluoxetine" and "randomised controlled trial" or "random allocation" or "double-blind method" or "meta-analysis" or "systematic review" or "overview" or "synthesis".

9.2 Summary of available estimates of comparative effectiveness

9.3 Fluoxetine and other selective serotonin reuptake inhibitors versus placebo

Systematic reviews in people aged 18 years or over in primary and secondary care found that ADs (tricyclic ADs, SSRIs, monoamine oxidase inhibitors (MAOIs), or venlafaxine) were effective for treatment of all grades of depressive disorders compared with placebo. However, the most robust available evidence of efficacy of treatment with ADs is in the pharmacological management of moderate and severe depression.

Four systematic reviews compared SSRIs with placebo in the acute treatment of depression. The first systematic review included five randomised controlled trials (RCTs) in people admitted to hospital (probably with severe depressive disorders), 40 RCTs in a setting outside hospital, one in both settings, and three that did not specify the setting (Joffe *et al.* 1996). All RCTs identified by the review were of at least 4 weeks' duration and included three way comparisons, including tricyclic ADs, SSRIs, or MAOIs and placebo. The review only included RCTs that measured improvement in depressive symptoms using validated scales such as the Hamilton Depression Rating Scale (HAM-D) and Montgomery-Asberg Depression Rating Scale. On average, 69% of people taking placebo had worse

outcomes over a mean of 6 weeks than the average person taking antidepressant drugs (mean effect size 0.5 for change in score with ADs *v* placebo). This review gave no information on adverse effects.

The second review compared newer ADs versus placebo for at least 6 weeks (Williams, Jr. *et al.* 2000). Response was defined as a 50% reduction in depression rating scale score or a Clinical Global Impression Scale (CGI) score of 1 (very much improved) or 2 (much improved). The review found that newer ADs significantly increased the proportion of people who responded compared with placebo (relative risk (RR) 1.6, 95% confidence interval (CI) 1.5 to 1.7). This review also performed a separate analysis of results for people in primary care (Mulrow *et al.* 2000). It found that results remained significant; the average response rate was 63% with newer agents, 35% with placebo, and 60% with TCAs (RR for SSRIs *v* placebo 1.6, 95% CI 1.2 to 2.1). In terms of overall tolerability, significantly more people taking SSRIs than placebo withdrew because of adverse effects.

The third review included 10 studies in which tricyclic ADs were compared with placebo, 3 in which SSRIs were compared with placebo, and 2 with both compared with placebo. Included studies were carried out in people with depression in primary care (Arroll *et al.* 2005). Both TCA and SSRI were significantly effective compared with placebo. For depression scores the standardized mean difference for tricyclics vs placebo was -0.42 (95% CI -0.55 to -0.3). The relative risk for improvement using tricyclics was 1.26 (95% CI 1.12 to 1.42). For SSRIs the relative risk for improvement was 1.37 (95% CI 1.21 to 1.55). According to this analysis, people taking TCAs (81/692) were more likely than people taking placebo (30/578) to withdraw because of adverse effects (RR 2.35, 95% CI 1.59 to 3.46). Similarly, people taking SSRIs (30/576) were more likely than people taking placebo (15/573) to withdraw because of adverse effects (RR 2.01, 95% CI 1.1 to 3.7).

In older adults one systematic review compared AD drugs versus placebo (Wilson *et al.* 2001). The review found that tricyclics, SSRIs, or MAOIs significantly reduced the proportion of people who failed to recover over 4–7 weeks compared with placebo (17 RCTs, 1326 people aged > 55 years).

Finally, one systematic reviews compared SSRIs with placebo in the maintenance treatment of depression. The review compared continuation treatment with prescription AD drugs versus placebo over 12 months in people who had responded to AD treatment over the previous 1 month to 3 years (Geddes *et al.* 2003). It found that, overall, continuing AD drugs in people who had responded to them significantly reduced the proportion of people who relapsed compared with

placebo (31 RCTs, 4410 people with first episode or recurrent depression; odds ratio (OR) 0.30, 95% CI 0.22 to 0.38). The review found that, in people who had responded to ADs after 2 months' treatment, the number needed to treat (NNT) by continuing ADs to prevent one additional relapse over 6 months was 6 (95% CI 5 to 8), to prevent relapse over 12 months 5 (95% CI 4 to 6), and over 18–36 months was 4 (95% CI 3 to 7). In people who had responded to ADs and received 4–6 months' treatment, the NNT by continuing ADs to prevent one additional relapse over 12 months was 7 (95% CI 5 to 8), and over 18–36 months was 3 (95% CI 3 to 4). The review found that relapse was most likely to occur in the first 12 months after AD discontinuation, but the benefits of continuing were apparent for up to 36 months.

9.4 Fluoxetine and other selective serotonin reuptake inhibitors versus tricyclic/heterocyclic antidepressants

Three systematic reviews found no significant difference in outcomes with different kinds of AD drug (tricyclic ADs, SSRIs, or MAOIs), although one systematic review found that SSRIs as a class were less effective than venlafaxine in increasing the proportion of people who responded, and that sertraline could be more effective than fluoxetine in terms of response rate.

The first review (63 RCTs, 6767 people) found no significant difference in overall symptoms between SSRIs and TCAs (mean effect size +0.03, 95% CI –0.02 to +0.09) (Geddes *et al.* 2000). The second review (95 RCTs, 10 533 people) found that SSRIs may be slightly more acceptable overall than tricyclics, as measured by the proportion of people who withdrew from clinical trials for any cause (RR 0.88, 95% CI 0.83 to 0.93) (Anderson, 2000). The third review (150 RCTs, ≥ 16 000 people) compared newer ADs versus tricyclics for at least 6 weeks (Williams, Jr. *et al.* 2000). Response was defined as a 50% reduction in depression rating scale score or a Clinical Global Impression Scale (CGI) score of 1 (very much improved) or 2 (much improved). The review found no significant difference between newer ADs and tricyclics in the proportion of people who responded (RR 1.00, 95% CI 0.97 to 1.06). The results were similar when the analysis was restricted to RCTs conducted in primary care (Mulrow *et al.* 2000).

Another systematic review compared fluoxetine with tricyclic ADs (Cipriani *et al.* 2005b). Defining as response the number of patients showing a reduction of at least 50% at the HDRS, this review found no statistically significant difference in terms of efficacy between fluoxetine and tricyclics as a class (PetoOR 0.95, 95% CI

0.80 to 1.14). In head-to-head comparisons, only dothiepin was significantly more effective than fluoxetine (PetoOR 2.09, 95% CI 1.08 to 4.05). Similarly, no statistically significant differences between fluoxetine and tricyclics, and between fluoxetine and individual comparator ADs were found on continuous outcome.

9.5 Fluoxetine and other selective serotonin reuptake inhibitors versus newer antidepressants

Two systematic reviews summarised the comparative evidence for use of second-generation ADs to treat major depressive disorder. The first review systematically evaluated comparative data on the efficacy, effectiveness, and tolerability of commonly prescribed second-generation ADs (SSRIs, bupropion, duloxetine, mirtazapine, and venlafaxine) (Hansen *et al.* 2005). Overall, these trials reported similar outcomes among the 6 SSRIs. Pooling together the six studies (774 patients) that compared paroxetine with fluoxetine and classified treatment response on the HAM-D scale, the rate of being a responder at study endpoint did not differ significantly between fluoxetine and paroxetine (RR 1.09, 95% CI, 0.97 to 1.21). This review also identified 5 studies (1190 patients) that compared fluoxetine with sertraline. Although no individual trial reported statistically significant findings, pooled results suggested a modest additional treatment effect (RR 1.10, 95% CI, 1.01 to 1.22) for sertraline compared with fluoxetine. The second review assessed the efficacy of fluoxetine compared to control agents in alleviating the acute symptoms of depression (Cipriani *et al.* 2005b). There was a statistically significant difference in terms of efficacy in favour of sertraline over fluoxetine, on a dichotomous outcome (PetoOR 1.40, 95% CI 1.11 to 1.76). Results on a continuous outcome were of borderline significance (standardised mean difference 0.10, 95% CI -0.01 to 0.21).

9.6 Summary of available estimates of comparative tolerability

In terms of tolerability one systematic review compared adverse events with SSRIs versus tricyclics in people aged 18 years or over with all severities of depression (Trindade *et al.* 1998). It found that about twice as many people taking tricyclics compared with SSRIs had dry mouth, constipation, and dizziness but that slightly more people taking SSRIs had nausea, diarrhoea, anxiety, agitation, insomnia, nervousness, and headache.

The systematic review that compared fluoxetine versus all other ADs (Cipriani *et al.* 2005b) found that in terms of patients who dropped out during the trial for any cause, fluoxetine was better tolerated than tricyclics (PetoOR 0.78, 95% CI 0.68 to 0.89). In particular, fluoxetine was better tolerated than amitriptyline (PetoOR 0.64, 95% CI 0.47 to 0.85) and imipramine (PetoOR 0.79, 95% CI 0.63 to 0.99). By contrast, dothiepin was better tolerated than fluoxetine (PetoOR 1.44, 95% CI 0.98 to 2.12). In terms of side effect profile, data from 26 RCTs showed that 50.9% of patients treated with fluoxetine experienced side effects during the study, in comparison with 60.3% of patients who received a tricyclic AD (RR 0.84, 95% CI 0.76 to 0.94, significantly favouring fluoxetine) (Brambilla *et al.* 2005). Additionally, the analysis of individual tricyclics showed that RR for side effects significantly favoured fluoxetine in comparison with amitriptyline and clomipramine, but not in comparison with the other tricyclics. In this review significant differences were reported as NNTs (positive NNTs indicating a significant advantage for fluoxetine, negative NNTs indicating a significant advantage for comparison). Tricyclics were associated with less insomnia (NNT -33, 95% CI -24 to -52), anxiety (NNT -105, 95% CI -55 to -1000), nausea (NNT -13, 95% CI -10 to -16), anorexia (NNT -100, 95% CI -56 to -434) and weight loss (NNT -23, 95% CI -14 to -55), but more sedation (NNT 21, 95% CI 16 to 30), dizziness (NNT 13, 95% CI 10 to 18), dry mouth (NNT 25, 95% CI 17 to 53), blurred vision (NNT 100, 95% CI 51 to 666), constipation (NNT 12, 95% CI 10 to 14) and weight gain (NNT 39, 95% CI 30 to 59) than fluoxetine.

Fluoxetine was similarly tolerated than other SSRIs in terms of patients who dropped out during the trial for any cause. However, fluoxetine was associated with less constipation (NNT 42, 95% CI 24 to 141), but more sweating (NNT -58, 95% CI -32 to -400) and weight loss (NNT -15, 95% CI -9 to -38) than paroxetine, and more nausea than fluvoxamine (NNT -5, 95% CI -2 to -71) (Cipriani *et al.* 2005b).

Another systematic review reported the mean incidence and 95% CIs for specific adverse events that were commonly reported in included RCTs (Hansen *et al.* 2005). Authors reported the following figures for fluoxetine: diarrhea (mean incidence 11.7, 95% CI 6.8 to 16.6), dizziness (mean incidence 7.2, 95% CI 4.3 to 10.0), headache (mean incidence 16.6, 95% CI 10.2 to 23.0), insomnia (mean incidence 13.7, 95% CI 10.0 to 17.4), nausea (mean incidence 18.6, 95% CI 15.1 to 22.1).

One large cohort study of people receiving four different SSRIs in primary care in the UK found that reports of common adverse events (nausea/vomiting, malaise/lassitude, dizziness, and headache/migraine) varied between SSRIs

(fluvoxamine 78/1000 participant months; fluoxetine 23/1000 participant months; RR *v* fluvoxamine 0.29, 95% CI 0.27 to 0.32) (Mackay *et al.* 1997). Only 52% of people responded to the questionnaire, although this response rate was similar for all four drugs. A study of spontaneous reports to the UK Committee on Safety of Medicines found similar safety profiles among the same four SSRIs (Price *et al.* 1996).

One RCT in people aged 18 years or over compared abrupt discontinuation of fluoxetine (96 people) versus continued treatment (299 people) in people who had been taking the drug for 12 weeks (Zajecka *et al.* 1998). Abrupt discontinuation was associated with increased dizziness (7% with abrupt discontinuation *v* 1% with continued treatment), dysmenorrhoea (3% *v* 0%), rhinitis (10% *v* 3%), and somnolence (4% *v* 0%). However, there was a high withdrawal rate in this RCT because of the return of symptoms of depression (39%), so these may be underestimates of the true rate of withdrawal symptoms. Between 1987 and 1995 the rate of spontaneous reports of suspected withdrawal reactions per million defined daily doses to the World Health Organization Collaborating Centre for International Drug Monitoring was higher for paroxetine than for sertraline and fluoxetine (Stahl *et al.* 1997). The most common withdrawal effects were dizziness, nausea, paraesthesia, headache, and vertigo.

9.7 SSRIs and suicide/deliberate self harm

There remains uncertainty about the safety of SSRIs, which may cause worsening of suicidal ideas in vulnerable people. Regulatory authorities in Europe, the UK, and the USA have issued warnings about the use of SSRIs in children and adolescents. The European Medicines Agency (EMEA) has ruled that SSRIs and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) should not be prescribed for depression for children and adolescents under the age of 18 years. The Committee for the Safety of Medicines in the UK has advised that the balance of risks and benefits for the treatment of depression in the paediatric population is unfavourable for paroxetine, citalopram, sertraline, venlafaxine, escitalopram, and mirtazapine. The regulatory authority in the USA requires a safety warning in bold text about suicide risk in package inserts for all antidepressants.

Two systematic reviews analysed suicidal ideas and completed suicides in randomised trials of AD drugs. Fergusson and colleagues conducted a systematic review of published RCTs comparing SSRIs with either placebo or other active treatments in patients with depression and other clinical conditions (Fergusson *et*

al. 2005). They found an almost two-fold increase in the odds of fatal and non-fatal suicidal attempts in SSRI users compared with users of placebo or other therapeutic interventions (excluding tricyclics). No increase in risk was observed, however, when only fatal suicidal attempts were compared between SSRIs and placebo. Finally, no differences were observed when overall suicide attempts were compared between SSRI and tricyclic users. By contrast, Gunnell and colleagues included in their review both published and unpublished RCTs submitted by pharmaceutical companies to the safety review of the Medicine and Healthcare products Regulatory Agency (MHRA) (Gunnell *et al.* 2005). These trials compared SSRIs with placebo in adults with depression and other clinical conditions. Three outcome measures were studied: completed suicide, non-fatal self-harm and suicidal thoughts. No evidence for an increased risk of completed suicide was found, and their analysis found only weak evidence of an increased risk of self-harm, and inconclusive evidence of an increased risk of suicidal thoughts (estimates compatible with a modest protective or adverse effect).

In addition to randomised trials, several case-control studies have contributed to shed light on this compelling issue. Jick and colleagues, who carried out a matched case-control study of more than 2500 patients using the UK General practice Research Database (GPRD), reported that the risk of suicidal behaviour after starting antidepressant treatment is similar among users of amitriptyline, fluoxetine, and paroxetine compared with the risk among users of dothiepin (Jick *et al.* 2004). However, dothiepin might not be a relevant reference AD for countries where this agent has never been licensed, such as Italy and the US (Barbui, 2004). This criticism led to a new analysis that used amitriptyline as reference compounds (Jick *et al.* 2004). The ORs (with confidence intervals) for non-fatal suicidal behaviors among users of the other 3 ADs were: dothiepin, 1.21 (0.80-1.83); fluoxetine, 1.40 (0.92-2.13); and paroxetine, 1.55 (0.99-2.43). A borderline value for paroxetine in comparison with amitriptyline emerged in this post-hoc analysis, leaving the possibility of an increased risk of nonfatal suicidal behaviors in users of this agent.

Using the GPRD, Martinez and colleagues analysed the risk of non-fatal self-harm and suicide in patients with a new diagnosis of depression who were prescribed SSRIs or tricyclics (Martinez *et al.* 2005). The cohort included 146,095 patients. In comparison with tricyclic users, SSRI users were not at increased risk of suicide or non-fatal self-harm; however, in patients aged 18 or less, weak evidence suggested a higher risk of non-fatal self-harm in those prescribed SSRIs.

Very recently, suicide risk during antidepressant treatment was assessed in the US by Simon and colleagues (Simon *et al.* 2006). Computerised health plan records were used to identify more than 65,000 individuals with more than 82,000 episodes of antidepressant treatment. The risk of suicide during acute-phase treatment was one in 3,000 treatment episodes, and risk of serious suicide attempt was one in 1,000. Data did not indicate a significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs.

Finally, a matched case-control study was carried out to estimate the relative risk of suicide attempt and suicide death in severely depressed children and adults treated with antidepressant drugs vs those not treated with antidepressant drugs (Olfson *et al.* 2006). Medicaid beneficiaries from all 50 states who received inpatient treatment for depression, excluding patients treated for pregnancy, bipolar disorder, schizophrenia or other psychoses, mental retardation, dementia or delirium, were included. Controls were matched to cases for age, sex, race or ethnicity, state of residence, substance use disorder, recent suicide attempt, number of days since hospital discharge, and recent treatment with antipsychotic, anxiolytic/hypnotic, mood stabilizer, and stimulant medications. The main outcome measures were suicide attempts and suicide deaths. In adults (aged 19-64 years), antidepressant drug treatment was not significantly associated with suicide attempts (OR 1.10, 95% CI 0.86 to 1.39) or suicide deaths (OR 0.90, 95% CI 0.52 to 1.55). However, in children and adolescents (aged 6-18 years), antidepressant drug treatment was significantly associated with suicide attempts (OR 1.52, 95% CI 1.12 to 2.07) and suicide deaths (OR 15.62, 95% CI 1.65 to infinity). In these high-risk patients, antidepressant drug treatment does not seem to be related to suicide attempts and death in adults but might be related in children and adolescents. These findings support careful clinical monitoring during antidepressant drug treatment of severely depressed young people.

10. Summary of available data on comparative cost and cost-effectiveness

The main disadvantage of the SSRIs when they were first introduced was the very significant difference in price between them and the tricyclics, an issue of less importance now as they come off patent, but one which remains important as other generations of AD drugs become available. A systematic review of economic analyses comparing any groups of ADs found only three published RCTs with economic analyses (Barbui *et al.* 2003). These show few differences between ADs in terms of total health care costs.

An alternative study design – the database analysis – has been much more widely published, almost always with direct support from individual pharmaceutical companies. Database analyses use large administrative healthcare databases to compare costs between individuals newly prescribed different ADs. Database analyses have many inherent methodological weaknesses (Hotopf and Barbui, 2005). Firstly, nothing is known about actual outcome, other than future health care use. Secondly, the design is not randomised, so it is possible that confounders – known or unknown – are responsible for any differences observed. For example it may be that individuals prescribed tricyclics have more severe depression, or previous episodes for which tricyclics had been prescribed. Such patients would be expected to have a worse outcome, making tricyclics appear more expensive than they would otherwise be. Thirdly, as a retrospective nature of these analyses mean that it is often very hard to follow the analytic strategy used. This means that investigators perform multiple analyses using different endpoints, and subtly different methods, to calculate costs. Although the systematic review found few consistent patterns in these studies, what was striking was the finding that the supporting company never seemed to publish evidence against their own AD. In four database analyses comparing sertraline with fluoxetine, three (all funded by the manufacturer of fluoxetine) found fluoxetine was associated with lower overall healthcare costs. The fourth study, funded by the manufacturer of sertraline, found sertraline was cheaper.

Very recently, two RCTs assessed he cost-effectiveness of tricyclics and SSRIs in primary care. Serrano-Blanco and colleagues, who carried out a six-month randomised prospective naturalistic study comparing fluoxetine to imipramine in three primary care health centres, randomised 103 patients: 38.8% (n = 40) were diagnosed with major depressive disorder, 14.6% (n = 15) with dysthymic disorder, and 46.6% (n = 48) with depressive disorder not otherwise specified (Serrano-Blanco *et al.* 2006). Patients with major depressive disorder or dysthymic disorder achieved similar clinical improvement in both treatment groups. However, for patients with major depressive disorder and dysthymic disorder, the imipramine group had fewer treatment-associated costs (imipramine 469.66 Euro versus fluoxetine 1,585.93 Euro in major depressive disorder, $p < 0.05$; imipramine 175.39 Euro versus fluoxetine 2,929.36 Euro in dysthymic disorder, $p < 0.05$).

In contrast with these findings, Kendrick and colleagues, who designed an open-label, three-arm randomised trial to determine the relative cost-effectiveness of tricyclics, SSRIs and lofepramine in UK primary care, found no significant differences in effectiveness or cost-effectiveness (Kendrick *et al.* 2006).

11. Methodological concerns in antidepressant trials

Is the evidence from AD RCTs reliable? Most trials comparing TCA with SSRIs are remarkably homogenous in design, generally comparing moderately depressed outpatients at six weeks, and mainly using the Hamilton Depression Rating Scale (HRSD) as an endpoint. The homogeneity of the trial designs means that within the limits of the primary research the use of meta-analysis is probably reasonable. A more serious concern is that of publication bias.

Funnel plots should be able to help us here. They work on the assumption that researchers are less likely to leave unpublished the results of large trials, than they are with small trials. A graph plotting the number of participants in the study (on the Y axis) against the effect size (on the X axis) will show an asymmetrical pattern if there is significant publication bias, with small "negative" studies (i.e. ones which favour the older comparison agent) being conspicuous by their absence. For the meta-analyses of tricyclics and SSRIs the funnel plots have generally been symmetrical, suggesting publication bias is absent. But should that reassure us? The funnel plot may give a very clear answer when there have been "mega-trials" comparing two treatments (ie studies with thousands of participants), as mega-trials are unlikely to go unpublished. For the AD trials there is not much spread in sample size between the largest and smallest trial.

Recent disclosures that GlaxoSmithKline deliberately "buried" two unfavourable randomised controlled trials giving key data on children and adolescents with major depression suggests that publication bias may remain a very serious limitation to the entire literature comparing SSRIs and tricyclics (Parker *et al.* 2003). If industry is prepared to conceal crucial safety and efficacy information on the treatment of children with depression with their compounds for purely commercial reasons, it is plausible that the same companies will have been as unscrupulous with data in adults. Furthermore, the publication bias on the paroxetine trials in children was not limited to small poorly conducted trials and as the recent systematic review for the UK National Institute of Clinical Excellence shows, the two unpublished trials were each bigger than the smaller (but commercially favourable) published trial (Whittington *et al.* 2004). The funnel plot (and other formal statistical tests which work on the same principle) would not be able to detect publication bias under these circumstance.

In addition to the problem of selective publication, Melander and colleagues highlighted that multiple publication is another strategy to give visibility to some

information only, making any attempt to recommend a specific SSRI from the publicly available data only is likely to be based on biased evidence (Melander *et al.* 2003).

This also raises a concern about the purpose of many of these trials. The sample sizes of most such trials is so small that highly clinically significant differences between agents simply could not have been detected (Barbui and Hotopf, 2001). Thus even if the newer ADs performed no better than placebo, many of these trials would have indicated no statistically significant difference when compared with the reference compound. Unfortunately this is often not reflected in the conclusion of the trials, which tend to be that the newer agent is as effective as the old one. These trials are effectively a form of marketing, and are often used to highlight a particular advantage of the new drug over the old, which may have been a type I error.

There is evidence of other forms of bias in randomised trials. For example, if one looks at all trials comparing fluoxetine and other ADs, and then categorises them according to whether fluoxetine was the new agent or the comparator, fluoxetine is slightly more effective when it is the new agent. In other words there is evidence of the so-called "wish bias" in which possibly due to observer bias, or publication bias, the drug performs better when it is new than when it is old (Barbui *et al.* 2002; Barbui *et al.* 2004). In addition fluoxetine tended to be prescribed in higher doses when it was the new agent (Barbui *et al.* 2002; Barbui *et al.* 2004).

12. Summary of regulatory status of the medicine

Fluoxetine is available in generic form. Similarly, other SSRIs are available in generic form, including citalopram, paroxetine and sertraline, and these antidepressants may soon be joined by other drugs. The prescription of fluoxetine is not restricted to authorised prescribers (e.g. psychiatrists).

13. Proposed (new/adapted) text for the WHO Model Formulary

Indications

Fluoxetine is indicated in the acute and maintenance treatment of adult individuals with moderate to severe major depression.

Contraindications

Fluoxetine should not be prescribed in association with a monoamine oxidase

inhibitor (MAOI) or within 14 days of discontinuing MAOI therapy. Allow at least 5 weeks after stopping fluoxetine before starting an MAOI. Do not administer thioridazine with fluoxetine or within 5 weeks after fluoxetine has been discontinued.

Precautions

Pregnancy, lactation, patients < 18 years of age, elderly patients. History of allergic reactions, seizures, suicidal tendency, activation of mania/hypomania, Miocardial infarction or unstable heart disease, diabetes, severe renal or hepatic impairment, hypokalemia (following self-induced vomiting), hyponatremia, altered platelet function.

Side effects

Headache, nervousness, insomnia, drowsiness, fatigue or asthenia, anxiety, tremor, dizziness or lightheadedness, nausea, dry mouth, diarrhea, anorexia, excessive sweating. Less frequently, rash, pruritus, weight loss, sexual dysfunction, convulsions.

Interactions

See Contraindications. Warfarin (monitor PT). Lithium levels may be increased or decreased (monitor). Use cautiously with other CNS-active drugs (e.g. tryptophan), agents highly bound to plasma protein or metabolized by the P450 2D6 system. St. John's Wort (increase in undesirable effects).

Patient tips

Full therapeutic effect may be delayed until 4 or 5 weeks of treatment. May cause drowsiness, dizziness (NB driving). Restrict alcohol intake.

Supplied

20 mg tablet

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