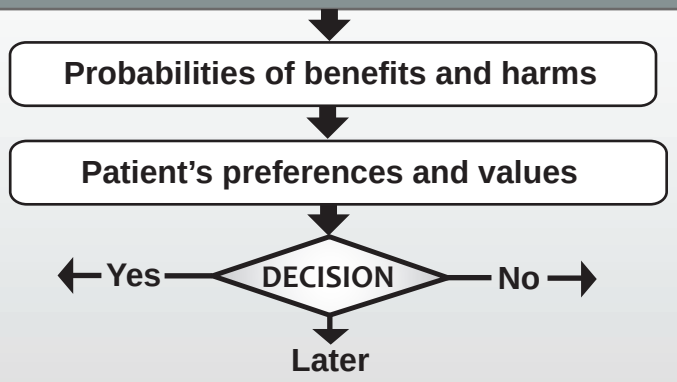
Selective serotonin reuptake inhibitors for the treatment of depression in adults



This document prepares the clinician to discuss scientific data with the patient so they can make an informed decision together.

Presenting selective serotonin reuptake inhibitors to patients

What are selective serotonin reuptake inhibitors (SSRIs) for?

- SSRIs are a class of medications that are taken daily **to reduce the symptoms of depression**. These medications (Citalopram [Celexa®], Escitalopram [Cipralex®], Fluoxetine [Prozac®], Fluvoxamine [Luvox®], Paroxetine [Paxil®], Sertraline [Zoloft®]) act by selectively inhibiting the uptake of serotonin.

Among individuals with depressive symptoms, who might consider taking SSRIs?

- Adults diagnosed with moderate to severe unipolar depression. Diagnosis can be made using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*

Why do patient preferences matter when making this decision?

- **There are pros and cons to taking this medication:**

PROS: Individuals with moderate to severe depression who take SSRIs for 4-8 weeks experience a small but clinically significant **reduction in their symptoms using the HRSD (see below)**.[1]

CONS: **85%** of individuals treated with SSRIs experience at least one **bothersome side effect**,[2] and **1-5%** of individuals **discontinue treatment** because of **reversible side effects** such as **sexual dysfunction** and **insomnia**.[3]

Hamilton Rating Scale of Depression (HRSD)**
- 17 to 21 item questionnaire to rate depression severity
- range: 0-50
- score > 18 indicates severe depression
- 3-point change: clinically significant

In the trials to evaluate the effectiveness of SSRIs, the **lengths of treatment were relatively short** – there is a lack of evidence on the effects of long term SSRI treatment.

- Moderate and severe depression can also be treated with **exercise,**[4] **behavioural and psychotherapy approaches, and other medications** such as tricyclic antidepressants and St. Johns wort.[5]

- **Both taking and not taking SSRIs are acceptable options, so we propose that:**
  1. the decision takes into account the **patient's preferences and values**
  2. the clinician **shares this decision** with the patient

* http://psychiatryonline.org/ and http://www.ncbi.nlm.nih.gov/books/NBK64063/
**http://imaging.ubmmedica.com/all/editorial/psychiatrictimes/pdfs/clinical-scales-ham-d-form.pdf

See page 2 for the current state of knowledge

DECISION BOX SSRI

State of knowledge – February 2013

Selection of best available studies

Benefits of medication

❶ Improves symptoms of depression

Individuals with moderate to very severe depression treated with SSRIs (paroxetine and fluoxetine) for 4-8 weeks **improve on average 3 points more** on the HRSD (range 0-50) than individuals receiving placebo.[1]

Harms of medication

❶ Adverse effects

85% of individuals treated with SSRIs experience at least one **bothersome side effect** during the first three months of treatment, and **55%** experience more than one.[2] The most common adverse effects experienced are:

- Sexual dysfunction
- Drowsiness
- Weight gain
- Insomnia
- Anxiety
- Dizziness
- Headache
- Dry mouth
- Nausea
- Rash

❷ Intolerable side effects

For each 100 individuals treated with SSRIs, **1-5 more (1-5%)** experience an **adverse event** causing them to **withdraw from treatment** compared to 100 individuals receiving placebo.[3]

☞ Grading of Recommendations Assessment, Development and Evaluation (**GRADE**)

How much confidence can we have in these results?

Symptoms of depression: **Moderate** Results are based on a meta-analysis of 21 trials (published and unpublished) submitted to the FDA for drug approval and are consistent across trials. The lengths of treatment and follow-up (4-8 weeks) are relatively short and effects might not apply to patients undergoing longer term treatment (decrease in quality of the evidence: -1). Most trials submitted to the FDA for drug approval are industry sponsored and we cannot rule out an overestimation of beneficial effects.[6]

Intolerable side effects: **Very low** Results are based on a systematic review of 3 good quality randomized controlled trials that are consistent with each other. However, the results are imprecise (decrease in quality of the evidence: -1) and the review comprises only published studies when we know that many studies remain unpublished (-1). The lengths of treatment and of follow-up (4-8 weeks) are relatively short and effects might not apply to patients undergoing longer term treatment (-1). All SSRI trials included in the meta-analysis were industry sponsored and we cannot rule out an underestimation of adverse effects.

☞ Questions to identify the patient's decision making needs:

- Do you have any questions about the benefits and harms of each option?
- Which benefits and harms matter most to you?
- Do you feel sure about the best choice for you?
- Who will support and advise you in making a choice?

Study descriptions and references:

1. **Kirsch et al**. PLOS Medicine 2008, DOI 10.1317. **Study design**: the Decision box team conducted a meta-analysis of 21 randomized controlled trials (RCT) of fluoxetine or paroxetine vs placebo, among the 35 trials reviewed. **Participants**: 849 adults with unipolar depression (17-30 on HRSD). **Length of treatment and follow-up**: 4-8 weeks.
2. **Hu et al.** J Clin Psychiatry 2004, 65 (7), 959-65. **Study design:** Cross sectional study using telephone interviews 75-100 days after initiating SSRI treatment. **Participants:** 401 adults (mean age 46) with major depression treated with SSRIs.
3. **Arroll et al.** Cochrane Database Syst Rev 2009, CD007954 (3) **Study design:** systematic review of 14 RCTs comparing treatment with trycyclic antidepressants or SSRIs with placebo. **Participants:** 2283 individuals (1060 in the 3 SSRI trials in the data presented in intolerable side effects), aged 15-65, from Australia, Canada, Europe, the UK and the US, diagnosed with a range of depressive disorders. **Length of Treatmen**t: 4-28 weeks (typically 4-8 weeks)
4. **Rimer et al.** Cochrane Database Syst Rev 2012, CD004366 (7). **Study design:** systematic review of 32 RCTs comparing exercise to standard treatment (e.g. pharmacotherapy), no treatment or a placebo. **Participants**: 1858 adults (mean age 22-88) from Canada, the US, Europe, Asia, Australia and New Zealand diagnosed with mild, moderate and major depression . L**ength of treatment**: 10 days to 16 weeks.
5. **Anderson et al**. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2000 British Association for Psychopharmacology guidelines. J. Psychopharmacol. 2008; 22(4); 343–396. **Study design**: Clinical practice guidelines developed through a literature review that judged the strength of the evidence in combination with clinical expertise.
6. **Turner et al**. New Engl J Med 2008,358, 252-60. **Study design**: systematic review of research literature that matched phase 2 and 3 clinical trials for 12 antidepressants that were FDA approved between 1987 and 2004. **Participants**: 12,564 adults.