

Evidence-based Practice Center Systematic Review Protocol

Project Title: *Depression Treatment after Unsatisfactory Response to SSRIs when used as First-line Therapy*

I. Background and Objectives for the Systematic Review

Depression is a complex mental illness that can result in significant disability, reduced quality of life, and societal burden. Pharmacological agents are one of several initial treatment modalities used for depression and one of the most frequently utilized classes of drugs are the selective serotonin reuptake inhibitors (SSRI). However, the rate of treatment response from baseline symptoms following first-line treatment with SSRIs is moderate, varying from 40 to 60 percent; remission rates vary from 30 to 45 percent.¹ Up to one third of persons on drug treatment will develop recurrent symptoms of depression while on therapy.² Moreover, there is limited evidence identifying reliable predictors (demographic, clinical, or genetic characteristics) of individual response.³ Adequate response to SSRI interventions is not consistently operationalized, but it is generally accepted that a 50 percent decrease in symptom severity from baseline is sufficient.⁴ Remission from depression is defined as being free or nearly free of symptoms for the current episode.

Given the large proportion of patients who do not respond adequately to SSRIs as first-line therapy, the practitioner is faced with the dilemma of determining the presence of inadequacy of the response and then selecting a new course of action. The new course of action may vary and can include: 1) an optimization strategy (altering dose or duration of the SSRI), 2) switching to other SSRIs, 3) switching to other classes of antidepressants, 4) combining SSRIs with other medications or non-pharmacological therapies 5) switching to non-pharmacological interventions alone, or 6) combinations of these.⁵ There is a need to examine the evidentiary base for these varying management strategies for patients who have failed to adequately respond to SSRI used as a first-line therapy for the index episode. For the purposes of this systematic review treatment failure (TF) is a response of less than 50 percent change relative to baseline and primarily reflects the perspective of the clinician and researcher; it marks the threshold of change by which a clinician will seek to progress or modify treatment for the patient. We use the terms “failure to respond” or “non-responder” in this same context. Unsatisfactory response is used in this review to capture the perspective of the patient being treated for depression; an unsatisfactory response may include other aspects of concern not captured by a change score relative to baseline.

TF can encompass a number of subgroups of patients who do not adequately respond to interventions for their current episode of depression. TF is not consistently defined within the literature, but is generally understood to reflect patients with depression who have not responded to one course of therapy. TF populations may include patients who would meet criteria for treatment resistance (≥ 2 inadequate responses) subgroups based on past treatment for prior episodes of depression.⁶ A portion of patients who have experienced TF will also go on to be defined as treatment resistant, if they also fail to respond to subsequent treatment strategies. Treatment resistance is variably defined but usually refers to patients who have failed at least

two trials of medication that have been of adequate dose and duration. Some definitions suggest that the failures should be to medications of different classes, but this is not universally accepted.

Monitoring adherence to antidepressants is sometimes difficult, but non-adherence may account for up to 20 percent of patients classified as having treatment resistant depression.⁷ Similarly, there is the potential for pseudo-resistance (non-response to inadequate treatment). All this would suggest the difficulty of defining and capturing subjects who have had TF and related subgroups. It may also reflect heterogeneity across studies evaluating the efficacy of SSRIs within this patient population.

Previous literature reviews would suggest that some of the strategies to treat patients following inadequate response may not be based on evidence; this is partially attributable to the small number of studies that have evaluated the different strategies. Rhue et al.⁸ evaluated the evidence for switching SSRIs in studies where 50 percent of subjects had previously used an SSRI and not responded adequately. This review found eight randomized trials and 23 open studies (with and without comparator groups). Response rates after switching to a new therapy varied from 12 to 86 percent and remission rates varied between 7 and 82 percent. Rates of dropouts due to harms varied from 9 to 39 percent. This review also identified some evidence showing that the number of failed responses to previous treatment with antidepressants was negatively associated with a positive response or outcome. Overall, this review showed that there was limited high quality evidence describing optimal strategies to switch medications in persons with previous SSRI use. In addition, there were limited studies that recruited prospectively determined SSRI non-responders. Papakostas et al.⁹ undertook a meta-analysis of four trials in subjects with TF who were randomized to switch to a non-SSRI versus another SSRI. The results suggest a modest and statistically significant advantage for remission rates when switching to non-SSRI rather than another SSRI. This review restricted eligible studies to those using three outcomes (Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, Quick Inventory of Depressive Symptomology) and to those evaluating the acute phase of Major Depressive Disorder (MDD). Williams et al.¹⁰ completed a systematic review on the treatment of depression in adolescents and children. Although this review did not focus on subjects who had failed to respond, the eligible studies did show that the rate at which children failed to respond to an initial trial of SSRIs varied from 31 to 64 percent. There was also some evidence that not all SSRIs were efficacious and that combined therapy (including an SSRI) is effective in this population.

A variety of treatment strategies aimed at helping individuals who have inadequate responses to first-line therapy with an SSRIs have been developed and applied in patients with depression. The primary goal of this CER is to examine the evidence guiding clinical treatment decisions and ultimately to aid clinicians in their care of patients in whom SSRI use as a first-line therapy for the index episode fails to bring about either complete or partial response or remission of depression.

II. The Key Questions

Question 1:

Among adults and adolescents with Major Depressive Disorder (MDD), Dysthymia, and Subsyndromal Depression, who are started on an SSRI and who are compliant with treatment but



fail to improve either fully, partially, or have no response, what is the benefit (efficacy or effectiveness) of monotherapy and combined therapy?

Population(s): The population will include adults (≥ 18 years) and adolescents (12 to 18 years) with Major Depressive Disorder (MDD), Dysthymia, or Subsyndromal Depression, who are compliant with treatment but who have failed to respond to the use of an SSRI for the index episode. These SSRIs include: fluoxetine, citalopram, fluvoxamine, sertraline, escitalopram, and paroxetine.

Persons with post-partum depression, bipolar depression, depressive psychosis, dysphoria, mourning syndrome, postoperative depression, premenstrual dysphoric disorder, pseudodementia, puerperal depression, seasonal affective disorder will be excluded.

- **Interventions:**

Monotherapy:

- a. Changing the dose or duration of the same SSRI
- b. Changing from one SSRI to another SSRI
- c. Changing from SSRI to another class of antidepressant
- d. Changing from SSRI to a non-pharmacologic therapy

Combined therapy:

- e. Adjunct therapy: augmentation by adding an adjunct drug (or supplement) that is intended to improve the response to the antidepressant (there is no formal indication for its use as a single agent for unipolar depression).
- f. Adjunct therapy: adding another antidepressant (other SSRI or class of antidepressant)
- g. Adjunct therapy: adding a non-pharmacological therapy
- h. Combinations of any of the interventions listed above or any other intervention

The pharmacological and non-pharmacological interventions of interest are as follows:

Selective-Serotonin Reuptake Inhibitors (SSRIs):

Fluoxetine (Fluoxetine Hydrochloride, Prozac, Prozac Weekly, Sarafem, Symbyax), Citalopram (Celexa, Citalopram Hydrobromide), Fluvoxamine (Fluvoxamine Maleate, Luvox, Luvox CR), Sertraline (Sertraline Hydrochloride, Zoloft), Paroxetine (Paroxetine Hydrochloride, Paxil, Paxil CR, Pexeva), Escitalopram (Escitalopram, Escitalopram Oxalate, Lexapro)

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs):

Duloxetine Hydrochloride (Cymbalta), Venlafaxine (Effexor, Effexor XR, Pristiq), Desvenlafaxine Succinate (Pristiq)

Monoamine oxidase inhibitors (MAOIs):

Phenelzine Sulfate (Nardil), Tranylcypromine Sulfate (Parnate), Emsam (Selegiline), Moclobemide (Manerix)

Non-SSRI Antidepressants:

Doxepin (Sinequan, Zonalon, Doxepin Hydrochloride), Clomipramine (Anafranil, Clomipramine Hydrochloride), Amitriptyline (Amitid, Amitril, Elavil, Endep, Etrafon 2-10, Etrafon 2-25, Etrafon-a, Etrafon-Forte, Limbitrol, Limbitrol DS, Perphenazine and Amitriptyline Hydrochloride combinations - Triavil 2-10, Triavil 2-25, Triavil 4-10), Maprotiline (Ludiomil), Desipramine (Norpramin, Pertofrane), Trimipramine (Surmontil, Trimipramine Maleate), Imipramine (Imipramine Hydrochloride, Imipramine Pamoate, Janimine, Pramine, Presamine, Tofranil, Tofranil-pm), Protriptyline Hydrochloride (Vivactil), Agomelatine (Valdoxan), Reboxetine (Edronax, Vestra)

Other Non-SSRI Antidepressants:

Trazodone (Desyrel, Trazodone Hydrochloride, Trialodine), Mirtazapine (Remeron, Remeron Soltab), Nefazodone (Nefazodone Hydrochloride, Serzone), Bupropion (Aplenzin, Bupropion Hydrochloride, Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban)

Non-pharmacological therapies:

Cognitive behavioral therapy (CBT), Interpersonal therapy (IPT), and other psychotherapies, Light therapy, Exercise, Complementary and Alternative Medicine (CAM) including Whole Body Systems (e.g., Acupuncture), Mind-Body Medicine (e.g., Meditation), Manipulative and Body-Based Practices (e.g., Massage), Energy Medicine (e.g., Reiki); Biologically Based Practices: Dietary supplements and herbal products (e.g., amino acids, vitamins and minerals, herbs, methyl-folate [Deplin], omega-3 fatty acids, SAME).

Augmenters:

Buspirone (Buspar), Gepirone (Ariza), Tansospirone (Sediel); Atypical Antipsychotics: Risperidone (Risperdal), Olanzapine (Zyprexa), Quetiapine (Seroquel), Aripiprazole (Abilify), Ziprasidone (Geodon); Psychostimulants: Amphetamine (Adderall), Methylphenidate (Ritalin); Dopamine agonists: Bromocriptine (Parlodel), Cabergoline (Dostinex), Pergolide (Permax), Pramipexole (Mirapex), Ropinirole (Requip), Apomorphine (Apokyn), Rotigotine (Neupro); Other drugs: Lithium, Pindolol, Tryptophan; Anticonvulsants: Carbamazepine (Tegretol), Sodium Valproate, Lamotrigine (Lamictal); Anti-Progestational agents: Mifepristone (Mifeprex); Sex Hormones: Androgens (e.g., Testosterone), Estrogens, Progesterone; Thyroid medications (triiodothyronine, T3).

- **Comparators:**

We will identify and include studies with comparative intervention groups. From a design hierarchy perspective, comparative group designs provide stronger evidence for efficacy and effectiveness than non-comparative designs.

The interventions (either alone or in combination) may be compared to any of the following:

1. Placebo
2. Same SSRI dose but different MDD population (for example, mild vs. severe MDD)
3. Same SSRI of different dose or duration
4. Other SSRI
5. Other antidepressant (from a different drug class)
6. Non-pharmacological therapies as described above
7. Adjunct therapy: combination of an augmenter plus SSRI
8. Adjunct therapy: combination of non-pharmacological therapy plus SSRI
9. Adjunct therapy: combination of augmenter and non-pharmacological therapy

- **Outcomes**

Primary Outcomes: Partial or complete response, Remission (free of all symptoms or with few symptoms), Speed of response or remission, and Relapse

Secondary Outcomes: Quality of life, Adherence, Return to work, Global change, External service utilization

- **Timing:** There are no restrictions on study eligibility with respect to a minimum treatment interval
- **Settings:** These will include studies with patients from primary care, outpatient, and inpatient mental health settings.

Question 2:

What are the harms of each of the monotherapy or combined therapies among these adults and adolescents? How do the harms compare across different interventions?

- **Population(s):** The population will include adults (≥ 18 years) and adolescents (12 to 18 years) with MDD, Dysthymia, or Subsyndromal Depression, who are compliant with treatment but who have failed to respond to the use of an SSRI for the index episode. These SSRIs include: fluoxetine, citalopram, fluvoxamine, sertraline, escitalopram, and paroxetine.
- **Interventions:** Monotherapy and combined therapies in the manner detailed above in KQ1). The main groups of interventions include the following: 1) SSRIs, 2) SNRIs, 3) MAOIs, 4) Non-SSRI Antidepressants, 5) Other Non-SSRI Antidepressants, 6) Non-pharmacological therapies and 7) Augmenter medications.
- **Comparators:** The interventions (either alone or in combination) may be compared to any of the following: 1) Placebo, 2) Same SSRI dose but different MDD population, 3) Same SSRI of different dose or duration, 4) Other SSRI, 5) Other antidepressant (from a different drug class), 6) Non-pharmacological therapy, 7) Adjunct therapy: combination of an augmenter plus SSRI, 8) Adjunct therapy: combination of non-pharmacological therapy plus SSRI, and 9) Adjunct therapy: combination of augmenter and non-pharmacological



therapy.

- **Outcomes:**

Harms: Treatment emergent symptoms as follows: Sexual dysfunction symptoms, Neuropsychiatric symptoms or sedation, Gastrointestinal disturbances, Weight gain or metabolic disturbance, Sleep disturbance, Cardiovascular system problems, toxicity problems, Other common adverse effects (for example, headaches)

- **Timing:** There are no restrictions on study eligibility with respect to a minimum treatment interval

- **Settings:** These will include studies with patients from primary care, outpatient, and inpatient mental health settings.

Question 3:

How do these therapies compare in different populations (for example, different depressive diagnoses, disease severity, ages, gender, racial and socioeconomic group, and medical or psychiatric co-morbidities)? These subgroups will be considered with respect to the different interventions.

- **Population(s):** The population will include adults (≥ 18 years) and adolescents (12 to 18 years) with MDD, Dysthymia, or Subsyndromal Depression, who are compliant with treatment but who have failed to respond to the use of an SSRI for the index episode. These SSRIs include: fluoxetine, citalopram, fluvoxamine, sertraline, escitalopram, and paroxetine.
- **Interventions:** Monotherapy and combined therapies in the manner detailed above in KQ1). The main groups of interventions include the following: 1) SSRIs, 2) SNRIs, 3) MAOIs, 4) Non-SSRI Antidepressants, 5) Other Non-SSRI Antidepressants, 6) Non-pharmacological therapies and 7) Augmenter medications.
- **Comparators:** The interventions (either alone or in combination) may be compared to any of the following: 1) Placebo, 2) Same SSRI dose but different MDD population, 3) Same SSRI of different dose or duration, 4) Other SSRI, 5) Other antidepressant (from a different drug class), 6) Non-pharmacological therapy, 7) Adjunct therapy: combination of an augmenter plus SSRI, 8) Adjunct therapy: combination of non-pharmacological therapy plus SSRI, and 9) Adjunct therapy: combination of augmenter and non-pharmacological therapy.
- **Outcomes:**
 - Primary Outcomes:* Partial or complete response, Remission (free of all symptoms or with few symptoms), Speed of response or remission, and Relapse
 - Secondary Outcomes:* Quality of life, Adherence, Return to work, Global change, External service utilization
 - Harms:* Treatment emergent symptoms as follows: Sexual dysfunction symptoms, Neuropsychiatric symptoms or sedation, Gastrointestinal disturbances, Weight gain or



metabolic disturbance, Sleep disturbance, Cardiovascular system problems, toxicity problems, Other common adverse effects (for example, headaches)

- **Timing:** There are no restrictions on study eligibility with respect to a minimum treatment interval
- **Settings:** These will include studies with patients from primary care, outpatient, and inpatient mental health settings.

Question 4:

How does the efficacy/effectiveness vary between the different monotherapies and combined therapies?

- **Population(s):** The population will include adults (≥ 18 years) and adolescents (12 to 18 years) with MDD, Dysthymia, or Subsyndromal Depression, who are compliant with treatment but who have failed to respond to the use of an SSRI for the index episode. These SSRIs include: fluoxetine, citalopram, fluvoxamine, sertraline, escitalopram, and paroxetine.
- **Interventions:** Monotherapy and combined therapies in the manner detailed above in KQ1). The main groups of interventions include the following: 1) SSRIs, 2) SNRIs, 3) MAOIs, 4) Non-SSRI Antidepressants, 5) Other Non-SSRI Antidepressants, 6) Non-pharmacological therapies and 7) Augmenter medications.
- **Comparators:** The interventions (either alone or in combination) may be compared to any of the following: 1) Placebo, 2) Same SSRI dose but different MDD population, 3) Same SSRI of different dose or duration, 4) Other SSRI, 5) Other antidepressant (from a different drug class), 6) Non-pharmacological therapy, 7) Adjunct therapy: combination of an augmenter plus SSRI, 8) Adjunct therapy: combination of non-pharmacological therapy plus SSRI, and 9) Adjunct therapy: combination of augmenter and non-pharmacological therapy.
- **Outcomes**
 - Primary Outcomes:** Partial or complete response, Remission (free of all symptoms or with few symptoms), Speed of response or remission, and Relapse
 - Secondary Outcomes:** Quality of life, Adherence, Return to work, Global change, External service utilization
 - Harms:** Treatment emergent symptoms as follows: Sexual dysfunction symptoms, Neuropsychiatric symptoms or sedation, Gastrointestinal disturbances, Weight gain or metabolic disturbance, Sleep, Cardiovascular system problems, Geriatric toxicity problems, Other common adverse effects (for example, headaches, orthostatic hypotension, and hypertension)
- **Timing:** There are no restrictions on study eligibility with respect to a minimum treatment interval
- **Settings:** These will include studies with patients from primary care, outpatient, and inpatient mental health settings.

Question 5:

What is the range of recommended clinical actions following the failure of one adequate course of SSRI based on current (< 5 years) clinical practice guidelines (CPGs)?

- **Population(s):** CPGs that provide recommendations for adults (≥ 18 years) and adolescents (12 to 18 years) with MDD, Dysthymia, or Subsyndromal Depression, who are compliant with treatment but who have failed to respond to the use of an SSRI for the index episode. These SSRIs include: fluoxetine, citalopram, fluvoxamine, sertraline, escitalopram, and paroxetine.
- **Interventions:** CPGs that provide recommendations on monotherapy and combined therapies in the manner detailed above in KQ1 following inadequate response to SSRI used as first-line therapy. The main groups of interventions include the following: 1) SSRIs, 2) SNRIs, 3) MAOIs, 4) Non-SSRI Antidepressants, 5) Other Non-SSRI Antidepressants, 6) Non-pharmacological therapies and 7) Augmenter medications.
- **Comparators:** CPG may not provide recommendations on comparator treatments.
- **Outcomes:** CPG may not identify key outcomes for their recommendations; if they do, then the following will be eligible.
 - Primary Outcomes:* Partial or complete response, Remission (free of all symptoms or with few symptoms), Speed of response or remission, and Relapse
 - Secondary Outcomes:* Quality of life, Adherence, Return to work, Global change, External service utilization
 - Harms:* Treatment emergent symptoms as follows: Sexual dysfunction symptoms, Neuropsychiatric symptoms or sedation, Gastrointestinal disturbances, Weight gain or metabolic disturbance, Sleep disturbance, Cardiovascular system problems, toxicity problems, Other common adverse effects (for example, headaches)
- **Timing:** There are no restrictions to the timing of the therapy recommendations from the CPG.
- **Settings:** These will include CPG recommendations for patients from primary care, outpatient, and inpatient mental health settings.

Summary of Revisions to Draft Key Questions:

The public comments were evaluated and discussed with the Task Order Officer and the Technical Expert Panel members. The following changes to the protocol were undertaken:

- 1) The project title was modified to clarify the language and avoid misinterpretation and the appearance of endorsement of SSRIs as the only option as a first-line therapy for depression.
- 2) The definition of terms was expanded to provide more detail for the primary outcome domains

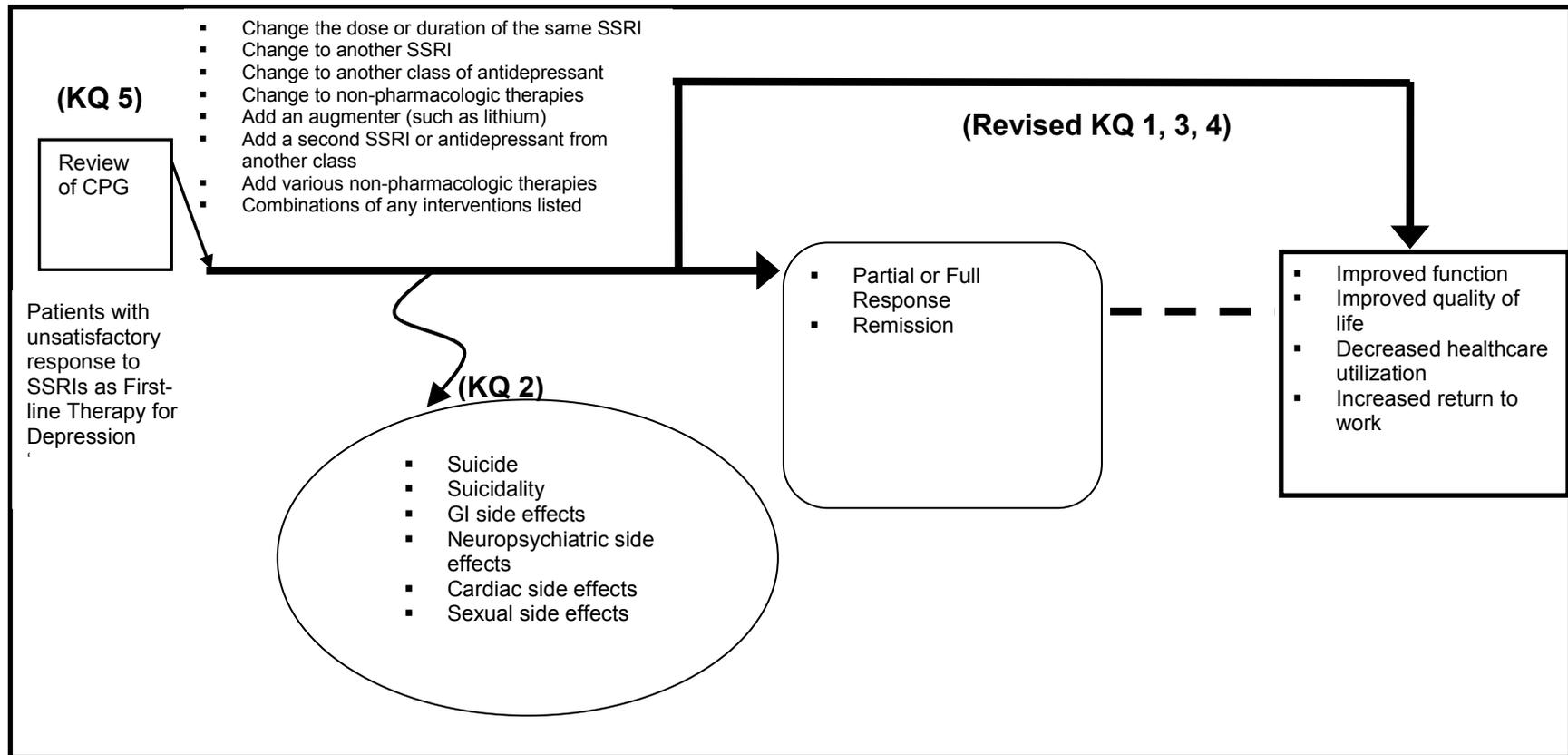


- 3) Some augmenters do have approval from some regulatory agencies for use with anti-depressants (for example, atypical antipsychotics). We have modified the language under the combined therapy intervention option to clarify this.
- 4) We have added quality criteria to assess treatment fidelity when evaluating psychotherapy interventions. We have expanded psychological therapies to include IPT, and other types of psychotherapy.
- 5) We have noted in the protocol that sleep disturbances, and use of alternative and complementary therapies will be extracted where reported in studies.
- 6) There is greater detail provided on the types of non-pharmacological therapies included.
- 7) A statement has been added to clarify how results will be grouped with respect to the different monotherapy and combined therapy interventions.

III. Analytic Framework

Figure 1 shows a flow diagram indicating the relationship between research questions in this CER. The first box in the figure shows the last question (KQ5) where current guidelines are reviewed. The other questions are related to interventions used following the unsatisfactory response to an SSRI for the index episode of depression. The treatment options following a failed response include the eight options (defined as interventions) for KQ1. Harms associated with any of these interventions are evaluated in KQ2 and can include suicide, sexual dysfunction, gastrointestinal effects and neuropsychiatric effects. The study effects are evaluated in KQ1, 3 and 4, with the latter two questions considering subgroups related to different population subgroups and different types of SSRIs. We note that intermediate outcomes, such as response and remission may precede quality of life or societal outcomes (costs, utilization).

Figure 1. Depression Treatment after Unsatisfactory Response to SSRIs when used as First-line Therapy



IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Target Population:

The population will include adults (≥ 18 years) and adolescents (12 to 18 years) with Major Depressive Disorder (MDD), Dysthymia, or Subsyndromal Depression, who meet the following criteria:

- currently on SSRI treatment for the index episode at the time of entry into the study
- have been judged to have had an “inadequate response” at the time of entry into the study
- The SSRIs that patients would not have responded to as a first-line therapy include the following: fluoxetine, citalopram, fluvoxamine, sertraline, escitalopram, and paroxetine
- OR
- The subjects who are recruited for entry into the study to be placed on an SSRI for purposes of monitoring prospectively the adequacy of their response; subsequent evaluation includes an intervention for those that have been shown to not respond adequately to the SSRI.

Exclusion

Subjects who are not receiving SSRI at time of entry into the study

OR

Subjects who are not recruited to evaluate adequacy of response prospectively

Persons with post-partum depression, bipolar depression, depressive psychosis, dysphoria, mourning syndrome, postoperative depression, premenstrual dysphoric disorder, pseudodementia, puerperal depression, seasonal affective disorder will be excluded.

Populations for whom the patho-physiological mechanism of depression is not comparable to those diagnosed with MDD including patients having initially sustained a cerebrovascular accident, Dementias (including Alzheimer’s disease, Vascular dementia), Parkinson’s Disease, Hypothyroidism, or Cushings’ Syndrome.

Target Intervention:

We have further defined the non-pharmacological therapies and Biologically Based Practices to include the following:

CBT, IPT, and other psychotherapies which may include: Behavior therapy, Interpersonal therapy (IPT), counseling, problem-solving therapy, psychodynamic therapy, bibliotherapy, guided self-help, distraction therapy

Light therapy (any therapy that includes primarily exposure to light)

Exercise (any type cardiovascular or strengthening or stretching and including yoga, hydrotherapy)

CAM therapies including:

- a) Whole System Medicines (e.g., Traditional Chinese Medicine),
- b) Mind Body Medicine (e.g., meditation/prayer, mental healing, engaging in pleasant activities, music therapy, art therapy, dance therapy),
- c) Manipulative and Body based Practices (e.g., massage),
- d) Energy Medicine (e.g., Biofields therapies (Reiki, Qi Gong) and bioelectromagnetic based therapies)
- e) Biologically Based Practices: Dietary supplements or herbal products (e.g., amino acids, vitamins and minerals, herbs such as borage, black flowers, carnitine, ginkgo biloba, ginseng, glutamine, inositol, chromium, lavender, lecithin, melatonin, selenium, saffron, St. John's wort, tyrosine, 5-HTP, s-Adenosylmethionine, phenylalanine, methyl-folate [Deplin], omega-3 fatty acids, SAME).

For clinical practice guidelines, we will focus on guidelines at a national level or from key professional organizations published in English but not limited to any country.

Sample size:

There are no restrictions for study sample size.

Study Design, and Publication types:

Inclusions: Full text reports as well as unpublished literature will be reviewed. Eligible study designs include:

Experimental studies with comparator groups (randomized and quasi-randomized trials).

Observational studies with comparator groups (retrospective and prospective cohort, case control, and interrupted time series with comparison group).

Letters with study data and abstracts

Exclusions:

All other study designs (for example, case series, qualitative studies).
Editorials, commentaries, and notes.

Language of Publication:

Review of non-English publications will be excluded for this review unless the TEP Panel brings forward evidence to suggest that there is a particular language of importance.

Contacting Authors for missing data:

Study authors will be contacted via email for missing outcome data or unpublished data (e.g., standard deviation).

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions.

Search Strategy

Studies will be limited to those published from 1980 forward when SSRIs first became available. The following databases were searched: MEDLINE; Cochrane CENTRAL, PsychINFO, Cochrane Database of Systematic Reviews; EMBASE; CINAHL; AMED. Strategies used combinations of controlled vocabulary (medical subject headings, keywords) and text words.

Grey literature will be identified through searching the websites of relevant specialty societies and organizations, Health Technology Assessment agencies (Hayes Inc. Health Technology Assessment), guideline collections, Regulatory information (i.e., United States Federal Drug Agency (FDA), Health Canada, Authorized Medicines for European Community), clinical trial registries (i.e., clinical.trials.gov, Current Controlled Clinical Trials, Clinical Study Results, WHO Clinical Trials), grants and federally funded research (i.e. National Institute of Health (NIH), HSRPROJ), Abstracts and conference proceedings (i.e. Conference Papers Index, Scopus), and the New York Academy of Medicine's Grey Literature Index.

Review of reference lists of eligible studies at full text screening will be undertaken. Any potentially relevant citations will be cross-checked with our citation database. Any references not found will be retrieved and screened at full text.

Our initial search strategy yielded approximately 60,000 citations and after removing duplicates across databases our final yield will approximate 45,000. Our search strategy was intended to be broad as our population is not well indexed and treatment failure is inconsistently defined within the literature. The search strategy was not delimited by treatments or outcomes. Additionally, our strategy included targeted searches specific to some terms for the non-pharmacological therapies and for adverse events related to the use of antidepressants. Note that in Embase alone there are over 7,000 articles that “focus” on adverse events relating to antidepressants, none of which would be excluded from this review. We expect that the vast majority of these 43,000 citations will not include our population; we will not be able to

determine this until they are screened as the population headings are not well indexed and there may be studies with subgroups of “failed response” subjects even though they are not the focus of the study.

Updating of the search

Just prior to submission of the draft report, an updating of our search in all specified databases (see above) will be undertaken.

Incorporation of Public and Peer Review suggestions for literature

Any publications suggested by peer reviewers or from public comment will be documented and verified within our citation database. Any references not included within our citation database will be retrieved and screened at full text.

C. Data Abstraction and Data Management

Relevant fields of information will be extracted from individual studies by trained data extractors using standardized forms and a reference guide. Prior to performing the data extraction, a calibration exercise will be conducted using a random sample of 10 included studies. Key study elements will be reviewed by a second person (study investigator) with respect to study outcomes, seminal population characteristics (past psychiatric history elements and definition of prior “treatment failure”), and characteristics of the intervention. Disagreements will be resolved by consensus.

Abstracted data will include study characteristics (e.g., first author, country of research origin, study design, sample size, sample size calculation or power estimate); clinical indications; and study duration or length of followup. Details of the patient population will include but not be limited to age, gender, racial composition, socio-economic status (income, education), sleeping disturbances or levels, co-morbidities (psychiatric and medical histories, use of alternative and complementary treatments concurrently or historically), definition of treatment failure, severity and duration of the depressive disorder. Details of the study intervention and comparator will include but will not be limited to type of intervention/comparator (pharmacological and non-pharmacological and the comparators as listed in the eligibility criteria above), dosage of intervention/comparator (type, dose, method of administration), frequency (number of treatments per week, number of total treatments, treatment fidelity for psychotherapy), treatment duration (total duration of care), duration of followup (from immediately post treatment to long term), and characteristics of treatment providers. Characteristics of the outcomes will include the type of instrument or scale, primary or secondary outcome status, type of effect measure (endpoint or change score, measure of variance (standard deviation, standard error), etc), definition of “adequate” treatment response, and type of statistical analysis (e.g., intention to treat).

D. Assessment of Methodological Quality of Individual Studies

We interpret methodological quality to include primarily elements of risk of bias, (systematic error) related to the design and conduct of the study. In addition, we will evaluate the

presence of additional biases, such as the funding bias, and a specific form of selection bias related to “treatment failure” being determined prospectively.

We have selected the Risk of Bias Tool by the Cochrane Collaboration¹¹ to assess randomized controlled trials. The tool contains 12 items that include evaluation of the domains of randomization, blinding, co-intervention, and selective outcome reporting biases. Criteria for evaluation are standardized for these domains. However, there is some evidence that certain items where greater judgment is required may be prone to inconsistencies amongst raters.¹² We will minimize inconsistency amongst raters by providing adequate training for raters and specifying clear decision rules in the standardized instructions.

We have selected the Newcastle Ottawa Quality Assessment Tool¹³ to assess risk of bias for observational studies. The study design elements evaluated with this tool include: selection of the study population, appropriate means for measuring exposures (case control studies) and outcomes (cohort studies), and comparability of groups (controlling for confounding). We will also evaluate potential biases related to funding sources or conflict of interest, as well as the determination of “treatment failure” prospectively.

Additionally, we will evaluate studies for adequacy of collecting and reporting harms using the McHarm Tool; this tool has been specifically designed for adverse events and captures domains related to the classification of harms, method of collection (active versus passive), and also the level of withdrawals due to adverse events.

We will judge experimental studies to be “fatally flawed” if allocation concealment, withdrawals, co-interventions, and adherence are all deemed inadequate. Studies that pass the first screening for fatal flaws will be classified into high or low risk of bias. A study with low risk of bias will be defined as a trial fulfilling six or more of the 12 methodological quality criteria in the Risk of Bias Tool and not having a fatal flaw. A study with high risk of bias will be defined as fulfilling fewer than six criteria and not having a fatal flaw. Similarly, studies with four or greater criteria on the NOS Tool will be considered to be high quality. We will wait to see the focus of the eligible observational studies (i.e., focus on outcomes of benefit or harm) in order to select the critical elements to specify that the study is fatally flawed. The classification of individual studies into categories of study limitations (high or low), will then be used to group studies for evaluation of the strength of the evidence.

E. Data Synthesis

Qualitative synthesis

For each trial, information on population characteristics (including history of treatment(s) for any previous episodes of depression, age of first diagnosis, etc.), study outcomes (both of benefit and of harm), sample size, settings, funding sources, treatments (type, dose, duration, and provider), methodological limitations, statistical analyses, and any important confounders will be summarized in text and summary tables. We will stratify results based on the depressive disorder (MDD, Dysthymia, and Subsyndromal depression) and by age (adolescents, adults, and elderly).

Additionally, we will group study results: a) according to the intervention categories under monotherapy and combined therapies; and b) the proportion of patients on SSRIs prior to the new intervention being evaluated. Within each category of interventions, we will attempt to stratify results based on the type of intervention.

Quantitative synthesis

The decision to pool individual study results will be based on clinical judgment with regards to comparability of study populations, treatments, and outcome measures. Specifically, methodological quality (e.g., high-risk of bias vs. low-risk of bias) and clinical diversity (e.g., study population gender, disease severity), treatment (type of intervention) and outcome characteristics (e.g., long-term follow-up vs. short-term followup, different measuring scales, different definitions of dichotomous outcomes) of individual studies will be considered. The extent of heterogeneity will be explored through subgroup and sensitivity analyses (described below).

We will use DerSimonian and Laird random-effects model to generate pooled measures of treatment effect (i.e., estimates of relative risk (RR) and standardized or weighted mean difference (SMD or WMD) with 95 percent confidence intervals (95 percent CIs). We will evaluate the extent of statistical heterogeneity using a Chi-square (statistically significant: $p \leq 0.1$) and I^2 (low: 25 percent moderate: 50 percent, and high: 75 percent) test statistics. The effect size will be calculated using the Kendal formula when continuous outcomes are reported as medians. We will separate studies by design type and only select like designs when meta-analysis is indicated.

We will attempt to pilot the software Meta-Analyst developed within AHRQ (Tufts University). If this proves to be unsatisfactory we will use STATA (Version 10, StataCorp, College Station, Texas, U.S.A.) If relevant numerical data (e.g., point effect estimate, standard deviation, standard error) is missing or is not reported adequately, we will attempt to calculate or impute the needed parameters where possible, as well as contact study authors. However, to maintain our timelines, we can only allow for a specified interval for responses.

Ideally we would hope to consider only direct comparisons between interventions of interest to specify our main conclusions. However, we cannot rule out the possibility of the need for computing and evaluating indirect comparisons; we will have to judge the feasibility of this once our final set of eligible studies has been established.

Subgroup and Sensitivity Analysis

There are key patient-specific or intervention-specific factors that may have an impact on the treatment effect and should be explored. Clinical heterogeneity will be assessed by considering any potential differences in participants amongst the trials (e.g., age, gender, diagnoses, disease severity, and definition of adequate response). Methodological heterogeneity will be explored by evaluating where studies failed criteria (particularly the method of defining treatment failure).

To maximize the similarities amongst studies that could potentially be combined for meta-analyses, we will further stratify where possible studies based on the: 1) depressive disorder (MDD, Dysthymia, and Subsyndromal depression), and 2) age categories (adolescents, adults, elderly (65 years and older). There are several patient characteristics that we may further explore with sensitivity analyses (if meta-analyses can be undertaken) including the following: 1) disease severity (within MDD only); 2) gender; 3) number of prior “treatment failures”; and 4) co-morbidities related to other psychological disorders. Additionally, if there are sufficient studies, we will explore trial specific factors such as: 1) duration or dose of intervention; 2) type of treatment provider; and 3) method of defining “adequate” response. Finally, we will attempt to explore the impact of key methodological study limitations, in particular: 1) percent of

withdrawals; 2) sample size; 3) high versus low overall quality; and 4) prospective determination of “treatment failure.”)

F. Grading the Evidence for Each Key Question

We will assess the overall strength of the body of the evidence using the GRADE approach.¹⁴ There are several factors that may decrease the overall strength of the evidence:

- 1) Study limitations (predominately risk of bias criteria)
- 2) Type of study design (experimental versus observational)
- 3) Consistency of results (degree to which study results for an outcome are similar; that is that variability is easily explained, range of results is narrow)
- 4) Directness of the evidence (assesses whether interventions can be linked directly to the health outcomes)
- 5) Precision (degree of certainty surrounding an effect estimate for a specific outcome)

There are factors recommended by the GRADE working group (e.g., burden of therapy, importance of the outcome being evaluated) that may be taken into consideration when assigning a GRADE category. These will be explicitly detailed for each outcome evaluated.

Publication bias

Although our search strategy is comprehensive and includes a grey literature search (including potential sources for unpublished trials), there is always the potential for publication bias. Publication bias is important to assess in reviews with the use of drugs, as there is evidence to suggest that industry sponsorship may lead to negative trials not being published¹⁵, that reporting of adverse events are more favorable to the funder,¹⁶ and that there may be delay in publication of negative findings.¹⁷ Thus, we will carefully scrutinize studies to determine the presence of selective non-reporting of outcomes (both of benefit and harm).

We will attempt to evaluate the presence of publication bias for primary outcomes with 10 or more studies using funnel plots, recognizing the limitations of interpreting the symmetry of these. If a particular outcome is shown to have a high risk of publication bias, then the analyses will be presented and the summary estimate will be interpreted with caution.

VI. Definition of Terms

Treatment Failure for this CER: Subjects who are currently on SSRI treatment for the index episode at the time of entry into the study and have been judged to have had an “inadequate response” at the time of entry into the study. Also, subjects who are recruited for entry into the study to be placed on an SSRI for purposes of monitoring prospectively the adequacy of their response; subsequent evaluation includes an intervention for those that have been shown to not respond adequately to the SSRI. Both these groups will be considered to have failed SSRI treatment.

Inadequate Response: Using a standardized instrument, an inadequate response is one where the subjects’ severity scores do not decrease (improve) by 50 percent.^{18,19} This term is

synonymous with **non responders or failure to respond**. These terms primarily reflect the perspective of the clinician or researcher.

Unsatisfactory Response: Reflects the patient's perception of their response to the intervention to treat their depression.

Remission: Remission from depression is defined as being free or nearly free of symptoms for the current episode.

Recurrence: Recurrence is defined as the return of a disease after its apparent cessation (symptoms return after a period of remission).

Relapse: Relapse is a return of symptoms satisfying the full syndrome criteria for an episode and which occurs following a period of remission but before recovery. Relapse is the point at which recurrent symptoms are severe enough that the clinician determines an intervention is warranted.

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VII. Summary of Protocol Amendments

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

For Comparative Effectiveness Reviews (CERs) the key questions are posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

It is our policy not to release the names of the peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.