Effective Health Care Program

Mental Health
Depression

Treatment for Depression After Unsatisfactory Response to SSRIs in Adults and Adolescents

Research Focus for Clinicians

A systematic review of 44 clinical studies published between January 1980 and April 2011 examined the comparative effectiveness, benefits, and adverse effects of interventions for adults and adolescents with major depressive disorder (MDD) who have an unsatisfactory response to treatment with a selective serotonin-reuptake inhibitor (SSRI). The review also compared recommendations from 27 Clinical Practice Guidelines (CPGs) published from January 2004 to April 2011. The findings of this review do not apply to subjects who have a primary diagnosis of bipolar disorder, schizophrenia, or anxiety disorder. This summary is provided to inform discussions of options with patients and to assist in decisionmaking along with consideration of a patient's values and preferences and should not be construed to represent clinical recommendations or guidelines. The full report is available at www.effectivehealthcare.ahrq.gov/ssri-depression.cfm.

Background

Although patients with MDD have a 63-percent response rate during 6 to 12 weeks of treatment with second-generation antidepressants, 53 percent do not achieve remission.[1,2]

Up to two-thirds of adult patients will not achieve remission with an SSRI.[3] SSRIs are a frequently used class of second-generation antidepressants.

Clinicians are faced with a number of treatment options (see Table 1) after an inadequate response to an SSRI, including both monotherapy and combination therapy approaches.

Monotherapy approaches include:

- Optimizing the dosage or duration of the current SSRI
- Switching to another SSRI or another antidepressant
- Switching to a nonpharmacological treatment (e.g., psychological therapies or exercise)

Combination therapy approaches include:

- Adding medications (e.g., augmenting agents, a different SSRI, or other antidepressants)
- Switching to another agent (e.g., a different SSRI) and adding another medication
- Adding a nonpharmacological treatment
- Combinations of these treatments

[1] Gartlehner G, et al. Ann Intern Med. 2011;155:772-85. PMID: 22147715.

[2] First-generation antidepressants may include tricyclic antidepressants and monoamine oxidase inhibitors. More recently developed second-generation antidepressants include SSRIs, selective serotonin and norepinephrine reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and other second-generation antidepressants (bupropion, nefazodone, and trazodone).

3Perahia DG, et al. J Psychiatr Res. 2009;43(5):512-8. PMID: 18707693.

In the studies included in the systematic review, the definition of an adequate response to SSRI medications is not consistent but generally refers to a 50-percent decrease in symptom severity. Remission from depression is defined as being free or nearly free of symptoms for the current episode. The systematic review evaluated treatment options for patients who only had a partial response or who had no response to an SSRI medication.

Conclusion

Evidence remains limited to support clinical decisionmaking about the available approaches for treating patients with MDD who have an inadequate response to SSRIs. For adults with MDD, evidence is insufficient to guide decisionmaking for comparisons among monotherapies, monotherapies versus combination therapies, and comparisons among combination therapies with a few exceptions. Adding an atypical antipsychotic—risperidone or olanzapine—to ongoing SSRI treatment may slightly improve response and remission rates when compared with continuing SSRI treatment alone. Low-level evidence suggests that comparable response and remission rates are obtained from switching to a new antidepressant versus combining the new antidepressant with pharmacological or nonpharmacological treatment. For adolescents with MDD, low-level evidence suggests that combining an antidepressant and cognitive behavioral therapy (CBT) may be superior to medication alone. For adults, most reported adverse effects were consistent with those typically associated with antidepressant use. Comparative evidence is insufficient to guide decisionmaking about adverse effects both in adults and in adolescents.

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Analysis of Clinical Practice Guidelines

Variations among CPGs reflect the great amount of uncertainty that exists in the current evidence base. Of the 27 CPGs reviewed (January 2004 to April 2011), most do not define "inadequate response." All 27 CPGs provide recommendations for patients with MDD, but 7 do not provide any recommendations for patients with previous inadequate responses to therapy.

When an increase in dose or duration is recommended for adults, the change in dose or duration is not specified. When switching to a different monotherapy agent is recommended, most CPGs do not mention a specific antidepressant. When combination therapy is recommended, the CPGs are more likely to specify the drug to add to the antidepressant, but there is great variability in the augmenting agents recommended. For adolescents, nonpharmacological interventions are the preferred first-line therapy. However, some CPGs cite research done in adult populations as the basis for treatment strategies in children and adolescents.

Clinical Bottom Line

For adults with MDD who have an inadequate response to SSRIs:

Optimizing SSRI therapy or switching monotherapy agents

Evidence is insufficient to determine if differences exist in response and remission rates if the current SSRI treatment is maintained versus:

- Dose escalation of the current SSRI ○○○
- Switching to a different SSRI ○○○
- Switching to a non-SSRI antidepressant ○○○
- Switching to a psychological intervention (e.g., CBT) ○○○

Monotherapy versus combination therapy: adding medications to the existing SSRI or to a new antidepressant

- Adding risperidone or olanzapine to ongoing SSRI treatment may slightly improve response and remission rates versus continuing SSRI treatment alone. ●○○
- Evidence is insufficient to determine if there are differences in response and remission rates for continuing monotherapy with an SSRI versus:
  - Adding buspirone ○○○
  - Adding other augmenting agents (e.g., lithium or mianserin) ○○○
  - Adding a non-SSRI antidepressant (clomipramine, bupropion, or desipramine) ○○○
- Comparable results were achieved in response and remission rates for switching to a new antidepressant versus:
  - Combining the new monotherapy with another treatment (e.g., a new SSRI, a non-SSRI, or a nonpharmacological treatment) ●○○
  - Combining the new antidepressant with buspirone ●○○

Monotherapy versus combination therapy: adding nonpharmacological treatment

Evidence is insufficient to determine if there are differences in response and remission rates for continuing therapy with an SSRI versus combining that SSRI with:

- CBT ○○○
- Dialectical behavior therapy ○○○
- Exercise ○○○

(Continued in next column)

For adults with MDD who have an inadequate response to SSRIs: *(Continued)*

Combination therapies

- Evidence is insufficient to determine if there are differences in response and remission rates when an SSRI is given in combination with another SSRI, another antidepressant, an augmenting agent, or CBT. ○○○

Adverse effects in adults with MDD

- In general, most reported adverse effects were consistent with those associated with antidepressant use and were likely mild to moderate in nature; common adverse effects included headaches, dry mouth, dizziness, weight gain, sexual dysfunction, and fatigue.
- In adults with MDD, serious and severe adverse effects (e.g., suicidality) were not measured or not reported in most studies, so there is insufficient evidence to compare the adverse effects of various treatment approaches. ○○○

Adolescents with MDD

- For adolescents with MDD who have an inadequate response to SSRIs, adding CBT may be superior to an SSRI alone. ●○○
- In one study on adolescents, there were no significant differences in adverse effects for patients on an SSRI or venlafaxine with or without CBT, except for an increase in skin rashes and cardiovascular events in patients on venlafaxine.
- **The FDA has issued a warning about suicidality and antidepressant drugs.** There is an increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for MDD and other psychiatric disorders.

Strength of Evidence Scale

High:	●●●	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate:	●●○	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low:	●○○	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient:	○○○	Evidence is either unavailable or does not permit a conclusion.

Gaps in Knowledge

- Overall, few studies have evaluated the impact of different depressive diagnoses, disease severity, previous comorbidities, age, sex, and race on treatment outcomes.
- There is inconsistency between studies in the definition of "inadequate response" and in the distinction between response and remission.
- More studies are needed on the response and remission rates in children and adolescents to treatments subsequent to an inadequate SSRI response.
- Evidence is very limited on response and remission rates for patients with subsyndromal depression or dysthymia who have inadequate responses to an SSRI.

Additional Information

- For adults with dysthymia or subsyndromal symptoms who have an inadequate response to SSRIs, there is insufficient evidence to evaluate treatment approaches.
- There is some evidence that suggests that people with concurrent anxiety symptoms have less likelihood of achieving remission.
- There is some evidence that suggests that milder depression, less family conflict, and the absence of suicidal behavior are associated with greater likelihood of a positive treatment response in adolescents.

Table 1. Pharmacological and Nonpharmacological Interventions Studied in the Review

SSRIs*	■ Citalopram (Celexa®) ■ Escitalopram (Lexapro®) ■ Fluoxetine (Prozac®, Prozac Weekly®, Sarafem®, Symbyax®)	■ Fluvoxamine (Luvox®, Luvox CR®) ■ Paroxetine (Paxil®, Paxil CR®, Pexeva®) ■ Sertraline (Zoloft®)
Non-SSRI Antidepressants	■ Amitriptyline (Amitid®, Amitril®, Elavil®, Endep®, Etrafon 2-10, Etrafon 2-25, Etrafon-a, Etrafon-Forte, Limbitrol®, Limbitrol® DS, Perphenazine®, and Triavil 2-10, Triavil 2-25, and Triavil 4-10) ■ Bupropion (Aplenzin®, Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®, Zyban®) ■ Clomipramine (Anafranil®) ■ Desipramine (Norpramin®, Pertofrane®) ■ Desvenlafaxine (Pristiq®) ■ Doxepin (Sinequan®, Zonalon®) ■ Duloxetine (Cymbalta®)	■ Imipramine (Janimine®, Presamine®, Tofranil®, Tofranil-PM®) ■ Maprotiline (Ludiomil®) ■ Mirtazapine (Remeron®, Remeron SolTab®) ■ Phenelzine (Nardil®) ■ Protriptyline (Vivactil®) ■ Selegiline transdermal system (EMSAM®) ■ Tranylcypromine (Parnate®) ■ Trazodone (Desyrel®, Trialodine®) ■ Trimipramine (Surmontil®) ■ Venlafaxine (Effexor®, Effexor XR®)
Augmenting and Nonantidepressant Agents	■ Anticonvulsants ■ Antiprogestational agents ■ Dopamine agonists ■ Psychostimulants	■ Sex hormones ■ Thyroid medications ■ Other drugs such as buspirone (Buspar®), lithium, pindolol, and tryptophan
	Atypical Antipsychotics:**	
	■ Aripiprazole (Abilify®) ■ Olanzapine (Zyprexa®) ■ Risperidone (Risperdal®)	■ Quetiapine (Seroquel®) ■ Ziprasidone (Geodon®)
Nonpharmacological Therapies	■ Cognitive behavioral therapy ■ Exercise	■ Interpersonal therapy ■ Other psychotherapies

* Concomitant use of selective serotonin-reuptake inhibitors (SSRIs) in patients taking monoamine oxidase inhibitors (MAOIs; e.g., phenelzine [Nardil®], selegiline transdermal system [EMSAM®], tranylcypromine [Parnate®]) is contraindicated, as cases of serious and sometimes fatal reactions have been reported. These reactions have also been reported in patients who have recently discontinued an SSRI or other drugs that interfere with serotonin metabolism and have been started on an MAOI. For additional information, see the U.S. Food and Drug Administration (FDA) safety announcements at www.fda.gov.

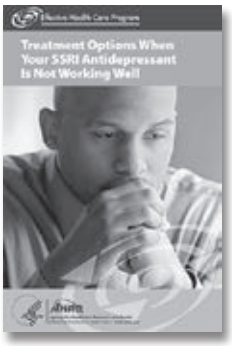
** Aripiprazole (Abilify®) and quetiapine XR (Seroquel XR®) have been approved by the FDA to be added to an antidepressant to treat adults with major depressive disorder. Olanzapine (Zyprexa®) has been approved by the FDA to be added to the SSRI fluoxetine (Prozac®, Prozac Weekly®, Sarafem®) to treat adults with treatment-resistant depression.

What To Discuss With Your Patients

- The health consequences of depression
- The rate of treatment response following treatment with SSRIs and the possibility of treatment-resistant depression
- The various interventions for treating depression after unsatisfactory response to SSRIs
- Patient preferences regarding cost, nonpharmacological treatment, medication type, and potential side effects
- What is known about nonpharmacological interventions for treating depression
- Potential drug interactions with medications
- The risk of antidepressants and other medications for pregnant or nursing women
- The possibility of severe adverse effects such as suicidality and that additional resources or help are available from the National Suicide Prevention Lifeline at www.suicidepreventionlifeline.org or 1-800-273-8255

Resource for Patients

Treatment Options When Your SSRI Antidepressant Is Not Working Well is a free companion to this clinician research summary. It covers:



- Background information about depression and unsatisfactory response to SSRIs
- Descriptions of the types of treatments, how they work, and potential side effects
- Questions to guide a discussion with you about treatment options

Ordering Information

For electronic copies of *Treatment Options When Your SSRI Antidepressant Is Not Working Well*, this clinician research summary, and the full systematic review, visit www.effectivehealthcare.ahrq.gov/ssri-depression.cfm. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

Source

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