



# Evidence-Based, Pharmacological Treatment Guideline for Depression in Korea, Revised Edition

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This paper aims to introduce, summarize, and emphasize the importance of the 'Evidence-Based, Pharmacological Treatment Guideline for Depression in Korea, Revised Edition'. The guideline broadly covers most aspects of the pharmacological treatment of patients in Korea diagnosed with moderate to severe major depression according to the DSM-IV TR. The guideline establishment process involved determining and answering a number of key questions, searching and selecting publications, evaluating recommendations, preparing guideline drafts, undergoing external expert reviews, and obtaining approval. A guideline adaptation process was conducted for the revised edition. The guideline strongly recommends pharmacological treatment considered appropriate to the current clinical situation in Korea, and should be considered helpful when selecting the appropriate pharmacological treatment of patients diagnosed with major depressive disorder. Therefore, the wide distribution of this guideline is recommended.

**Keywords:** Depression; Pharmacological Treatment; Guideline; Korea

## INTRODUCTION

Depression is a highly prevalent mental disease that is prone to recurrence and chronicity, and the WHO forecasted that this disease would be second only to heart disease as a cause of loss of healthy years by 2020 (1). Nevertheless, due to its pathological features, the treatment of depression has not been systematized, but is dependent on the experience of individual pathologists. As an attempt to overcome such circumstances, ceaseless efforts have been made worldwide for the development of an evidence-based clinical practice guideline that would suggest therapeutic recommendations systematically (2).

The treatment guideline development team judged that the Republic of Korea currently has, at least, the minimum infrastructure needed for producing an evidence-based clinical practice guideline. This decision was based on the improved national environment, in which rapidly growing information and communication networks now provide up-to-date knowledge on treatment, which can be accessed and applied efficiently. In 2005, the Republic of Korea Government began to take note of the seriousness of major depressive disorder (MDD) and realized that a guideline would be essential for the improved and systematic treatment of depression, and at last decided to build a national depression clinical research center as a national health and medical treatment technology infrastructure development project. Our research team developed the "Evidence-based, Pharmacological Treatment Guideline for Depression in Korea" in 2008 (3), and developed the "Evidence-based, Non-pharmacological Treatment Guideline for Depression in Korea" in 2010 (4). Due to the limitations of the initial pharmacological treatment guideline, the accumulation of new clinical information with time, and the emphasis on the importance of a guideline reflecting the current local clinical situation, the "Evidence-Based, Pharmacological Treatment Guideline for Depression in Korea, Revised Edition" was released in 2012 (5). In an attempt to inform Korean practitioners of the recommendations made in the revised edition,

papers reporting certain recommendations of the guideline were published in the Korean language (6-8). However, an introduction to the guideline as a whole has not yet been made, and no report on the guideline has ever been written in English. Therefore, the existence of a Korean evidence-based, pharmacological treatment guideline for depression has not yet been acknowledged outside Korea. To provide a broad introduction and wide distribution of this guideline, a summary of the guideline written in English has been greatly needed. Hence, the aim of this article is to introduce, summarize, and emphasize the importance of the “Evidence-Based, Pharmacological Treatment Guideline for Depression in Korea, Revised Edition”.

## HOW THE GUIDELINES WERE PREPARED

### Clinical practice guideline development group composition

The clinical practice guideline development group was composed of a multidisciplinary team from the Clinical Research Center for Depression, in order to expand their network to include psychiatrists, research administrators, clinical psychologists, and experts on systematic reviews, preventive medicine, and methodology. From key question selection to recommendation development the group members conducted comparative assessments of all the results at every phase while conducting the education or practice necessary for each phase, in an attempt to determine the scientific methods necessary for developing this evidence-based treatment guideline.

### Key question development

A treatment guideline is prepared by following a standard procedure that includes selecting clinical questions that need to be answered for the diagnosis and treatment of a specific disease or health problem, and by collecting and classifying this information and preparing the recommendations for the corresponding questions. Therefore, defining these key questions is the first step of collecting and evaluating evidence. This step is important, as it is the basis of the scientific evidence chosen to comprise the guideline. The key questions for this revised guideline were chosen from key questions that typically arise from the beginning until the end of the pharmacological treatment of a patient diagnosed with moderate to severe MDD according to the DSM-IV TR. In order for the questions to be answered accurately and correctly, the “PICO” method was used. The questions include the following four elements. P (patient population) represents patients or corresponding problems; I (intervention) represents the main intervention activities such as diagnostic procedures, prognostic factors, and treatment; C (comparison) represents comparative intervention; and O (outcome) represents the clinical result (9). The key questions broadly cover most aspects of the pharmacological treatment of MDD pa-

tients, such as the initiation of antidepressant treatment, efficacy and side effects of treatment, increase in drug dosage, and augmentation, combination, and switching of medication.

### Adaptation process

The clinical practice guideline adaptation manual (version 1.0) (10), which was originally developed by the ADAPTE Collaboration, translated under the official approval of the original Bureau of Clinical Research Support Center, and modified to fit the current clinical environment of Korea, was used for the adaptation and revision of this new guideline. The guideline went through most of the processes proposed in the modified manual.

### Search of treatment guidelines

A comprehensive search of the National Guideline Clearinghouse, NHS Evidence, Guidelines International Network, and PubMed was conducted. 2,526 articles were identified, and among them, only the guidelines prepared by governments, states, or learned societies were selected from the search list. Based on these inclusion criteria, 21 depression treatment guidelines were selected.

### Evaluation of treatment guidelines

The 21 studies on treatment guidelines for depression were selected and evaluated by a working group composed of a psychiatrist, a specialist on preventive medicine, and a clinical psychologist, using the AGREE II Tool. The selected studies were assessed for all of the 6 domains of AGREE II, that is, the scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. The total score was converted to a percentile, and depending on the converted scores, weighted values were assigned as follows: 3 points for a score 60 and above, 2 points for 40 and above but less than 60, 1 point for a score below 40. The points were then summed (with the total of 18 points). Among the studies, 12 articles were found to be of good quality and were finally selected as shown in Table 1. The consistency of the evidence itself, the interpretation of evidence, and the recommendations in each treatment guideline were reviewed. The scientific feasibility of the treatment guidelines was also reviewed and integrated by examining the validity, the standard level and the consistency of the evidence, and the concordance with other treatment guidelines.

### Recommendation grades

Expert panel meetings were held for the selection of recommendation statements. A total of 12 experts participated in the evaluation, scoring each statement on a scale of 1 to 9 (1, most inappropriate and 9, most appropriate). Panel meetings were held face to face after preliminary evaluation, results and problems were reviewed and the recommendations were amended, with

**Table 1.** Twelve clinical practice guidelines for depression

	Formal title, Development group, Year of publication, (Reference number)	Abbreviation
1	Identification of common mental disorders and management of depression in primary care, the New Zealand Guidelines Group, 2008 (14)	The New Zealand Guidelines Group guideline
2	Depression: the treatment and management of depression in adults (National clinical practice guideline 90), National Institute for Health and Clinical Excellence (NICE), 2009 (12)	NICE guideline
3	Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guideline, Canadian Network for Mood and Anxiety Treatments & Canadian Psychiatric Association, 2009 (17)	CANMAT guideline
4	Practice guideline for the treatment of patients with major depressive disorder, American Psychiatric Association (APA), 2010 (16)	APA guideline
5	Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2000 British Association for Psychopharmacology guidelines, British Association for Psychopharmacology, 2008 (13)	BAP guideline
6	Guideline on management of depression in primary care Hong Kong, Professional development & quality assurance prepared by a group of family physicians, 2005 (24)	Hong Kong guideline
7	Using second-generation antidepressants to treat depressive disorder: A clinical practice guideline from the American College of Physicians, American College of Physicians, 2008 (25)	ACP guideline
8	Clinical practice recommendations for depression, Northern Sydney Central Coast Mental Health Drug & Alcohol (NSCCMHDA) and University of Sydney CADE Clinic, 2009 (15)	NSCCMHDA and University of Sydney CADE Clinic guideline
9	Texas medication algorithm project procedural manual - major depressive disorder algorithms, Texas Department of Mental Health and Mental Retardation (TDMHMR) in collaboration with Texas universities, 2008 (26)	TDMHMR in collaboration with Texas universities guideline
10	World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders in primary care, International Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP), 2007 (21)	WFSBP guideline
11	Korean medication algorithm project for depressive disorder. Korean medication algorithm for depressive disorder 2008, Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology, 2008 (27)	Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guideline
12	Evidence-based, pharmacological treatment guideline for depression in Korea, Clinical Research Center for Depression, 2008 (3)	Clinical Research Center for Depression guideline

a second evaluation taking place (11).

### Treatment guideline preparation

Once the content of the adapted treatment guideline was decided upon, all past processes were recorded in the guideline draft in detail. The main principles of the drafting process are as follows: The process is transparent and accurate, the content of reference studies is reflected accurately and the studies are appropriately referenced, and it is acknowledged that the original treatment guideline developers have made great contribution. This guideline was prepared based on these principles.

### External expert review and approval

The guideline draft was reviewed by five experts (peer review), and the results of the reviews were also reflected in this guideline. A public hearing was held to collect the stakeholders' opinions. Finally the approval of the Korean Neuropsychiatric Association was obtained on April 13, 2011.

## KEY QUESTIONS AND RECOMMENDATIONS

**Key question 1.** What is the first-line treatment agent among antidepressants?

### Evidence

In order to be considered a first-line antidepressant, the antidepressant must have the same efficacy as tricyclic antidepressants (TCAs), a favorable tolerance level, and a high safety level even

when taken in large doses. As there is sufficient evidence that selective serotonin reuptake inhibitors (SSRIs) satisfy these qualifications, the New Zealand guidelines group, National Institute for Health and Clinical Excellence (NICE), British Association for Psychopharmacology (BAP), and the Clinical Research Center for Depression guidelines have strongly recommended SSRIs as a first-line treatment agent (3, 12-14). Furthermore, the Canadian Network for Mood and Anxiety Treatments (CANMAT), American Psychiatric Association (APA), and Northern Sydney Central Coast Mental Health Drug & Alcohol (NSCCMHDA) and University of Sydney CADE Clinic guidelines have recommended serotonin and norepinephrine reuptake inhibitors (SNRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs) and norepinephrine and specific serotonergic antidepressants (NaSSAs) as first-line antidepressants (15-17). TCAs are as effective as SSRIs; however, TCAs have many adverse effects, poor tolerability, and high discontinuation rates. Therefore, TCAs are not recommended as first-line treatment agents (18-20). However, patients with melancholic depression or patients who have responded well to TCAs previously are recommended to use TCAs as first-line treatment agents.

### Recommendations

SSRIs, SNRIs, NDRIs, and NaSSAs are strongly recommended as first-line treatment agents. However, TCAs are weakly recommended as first-line agents, depending on patient factors and medication costs.

**Key question 2.** Is there a difference in tolerability among antidepressants?

*Evidence*

The APA guideline described SSRIs as superior in their safety profile and tolerability (16). The BAP and World Federation of Societies of Biological Psychiatry (WFSBP) guidelines described SSRIs as having better tolerability than TCAs, and having a lower discontinuation rate (13, 21-23). In addition, the New Zealand guidelines group reviewed 13 studies on the effects of antidepressants and concluded that SSRIs were superior in tolerability to other antidepressants such as TCAs and venlafaxine (14).

*Recommendations*

In patients with low tolerability to antidepressant medication, SSRIs are weakly recommended as a treatment agent.

**Key question 3.** What factors influence the choice of antidepressant medication?

*Evidence*

The NICE, CANMAT, BAP, Hong Kong, ACP, NSCCMHDA and University of Sydney CADE Clinic, and WFSBP guidelines have recommended considering the potential side effects of the medication and previous history of side effects when on that medication (12, 13, 15, 17, 21, 24, 25). The APA, BAP, Hong Kong, ACP, and WFSBP guidelines have recommended considering the preference of and acceptability to the patient (13, 16, 21, 24, 25). The CANMAT, APA, Hong Kong, ACP, and WFSBP guidelines have also recommended considering the cost of treatment (16, 17, 21, 24, 25). Furthermore, the CANMAT guideline has also recommended considering the age, sex, severity of the illness, availability of medication, and discontinuation symptoms (17), while the BAP, NSCCMHDA and University of Sydney CADE Clinic, and WFSBP guidelines have recommended considering adherence to medication and family history of medication (13, 15, 21). Finally, the WFSBP guideline has also recommended considering the physician's experience with a given drug (15, 21).

*Recommendations*

It is strongly recommended that the potential side effects of the medication, patient history of having side effects when taking medication, drug interaction, previous treatment response, preference of and acceptability to the patient, cost of treatment, and co-existing diseases all be considered when selecting antidepressants.

**Key question 4.** Is there a difference in treatment efficacy depending on the type of depression?

**Key question 4-1.** Which antidepressant is most efficacious in the treatment of atypical depression?

*Evidence*

The New Zealand guidelines group recommended SSRIs for the treatment of atypical depression, and the NICE, APA, BAP, and NSCCMHDA and University of Sydney CADE Clinic guidelines recommended SSRIs and monoamine oxidase inhibitors (MAOIs) for the treatment of atypical depression (12-16). Moreover, the APA guideline recommended both MAOIs and SSRIs for the treatment of atypical depression (16); however, MAOIs may be unsuitable due to restrictions on intake of food while on medication.

*Recommendations*

SSRIs are weakly recommended for the treatment of atypical depression.

**Key question 4-2.** Which antidepressant is most efficacious in the treatment of psychotic depression?

*Evidence*

The NICE, CANMAT, APA, BAP, NSCCMHDA and University of Sydney CADE Clinic, Texas Department of Mental Health and Mental Retardation (TDMHMR) in collaboration with Texas universities, WFSBP, Clinical Research Center for Depression, and the Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have recommended the augmentation treatment of both antidepressants and antipsychotics rather than antidepressant monotherapy (3, 12, 13, 15, 16, 21, 25-27).

*Recommendations*

It is strongly recommended that antidepressants be augmented with antipsychotic medication in psychotic depression.

**Key question 4-3.** Which antidepressant is most efficacious in the treatment of seasonal depression?

*Evidence*

The NICE, CANMAT, APA, and BAP guidelines noted that taking bupropion may prevent major depressive episodes in the winter (12, 13, 16, 17). The BAP and WFSBP guidelines have recommended sertraline (28) and fluoxetine (29) for the treatment of seasonal depression (13, 21). The NICE guideline maintained that evidence on antidepressants being effective in treating seasonal depression is insufficient; however, the evidence supports that antidepressants are effective in preventing depression (12). The WFSBP guideline described SSRIs as having efficacy in treating seasonal depression; however, SSRIs take longer to treat symptoms than light therapy and have more side effects (13, 29, 30).

*Recommendations*

Although there is not much evidence on the efficacy of antidepressants in the treatment of seasonal depression, SSRIs and bupropion may be weakly recommended as a treatment modality.

**Key question 5.** Are antidepressants more efficacious than placebo?

**Key question 5-1.** Are TCAs more efficacious than placebo in the treatment of depression?

*Evidence*

The New Zealand guidelines group, NICE, APA, BAP, Hong Kong, WFSBP, Clinical Research Center for Depression, and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have all described TCAs to be superior to placebo in treating depression (3, 12-14, 16, 24, 27). However, the NICE guideline described TCAs as having more side effects than placebo and a higher discontinuation rate due to the side effects (12).

*Recommendations*

It is strongly recommended that TCAs are more efficacious than placebo in the treatment of depression.

**Key question 5-2.** Are MAOIs more efficacious than placebo in the treatment of depression?

*Evidence*

The NICE and APA guidelines have described moclobemide as more efficacious than placebo (12, 16). The NICE guideline reported that an HRSD score improvement of over 50% was superior to placebo (12). The APA guideline reported that 6 mg per day of transdermal selegiline for 6 weeks was shown to be more efficacious in 177 MDD patients compared to placebo (16, 31-33). The NICE guideline noted that evidence of tolerability is not sufficient (12).

*Recommendations*

It is strongly recommended that MAOIs are more efficacious than placebo in the treatment of depression.

**Key question 5-3.** Are SSRIs (including escitalopram) more efficacious than placebo in the treatment of depression?

*Evidence*

The New Zealand guidelines group, NICE, APA, BAP, Hong Kong, WFSBP, and Clinical Research Center for Depression guidelines have all described SSRIs to be superior to placebo in treating depression (12-14, 16, 21, 24). In particular, the NICE guideline

described SSRIs as having greater efficacy than placebo with HDRS improvement of more than 50%, with similar effects in moderate, severe, and extremely severe depression (12). The BAP guidelines described SSRIs as having a 61% response rate, whereas placebos had a 50% response rate (13). The WFSBP guideline also suggested as evidence, double-blind studies reporting SSRIs as being more efficacious than placebos (34, 35). However, the NICE guideline described the difference in remission rate to be non-significant, and although a significant difference was shown in moderate and extremely severe depression, the effect was not clinically relevant (12).

*Recommendations*

It is strongly recommended that SSRIs are more efficacious than placebo in the treatment of depression.

**Key question 5-4.** Are SNRIs (venlafaxine, duloxetine) more efficacious than placebo in the treatment of depression?

*Evidence*

The NICE and APA guidelines have described duloxetine and venlafaxine as being more efficacious than placebo (12, 16). Three studies that compared the efficacy of duloxetine and placebo reported duloxetine to be superior, and the effect size was also statistically superior. At the end of treatment, duloxetine seemed to be efficacious in the improvement of HDRS compared to placebo. However, pain associated with depression showed no significant difference. The discontinuation rate at the early stages of treatment was twice as high for duloxetine compared to placebo, but the discontinuation due to ineffectiveness was twice as high for placebo.

*Recommendations*

It is strongly recommended that duloxetine and venlafaxine are more efficacious than placebo in the treatment of depression.

**Key question 5-5.** Are NaSSAs (mirtazapine) more efficacious than placebo in the treatment of depression?

*Evidence*

The APA and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have described mirtazapine as having superior efficacy compared to placebo (16, 27). A meta-analysis comparing 6 studies reported that when mirtazapine was taken for 6-8 weeks, superior treatment efficacy was observed compared to placebo (36). Furthermore, the Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guideline identified mirtazapine as having superior antidepressant effects compared to placebo, based on many double-blind studies and meta-analyses (level 1) (27).

*Recommendations*

It is strongly recommended that mirtazapine is more efficacious than placebo in the treatment of depression.

**Key question 5-6.** Are NDRIs (bupropion) more efficacious than placebo in the treatment of depression?

*Evidence*

The APA and the Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines reported bupropion to be more efficacious than placebo (16, 27). Bupropion showed superior efficacy in the treatment of depression in the acute phase compared to placebo (37), and all three forms of bupropion are more efficacious than placebo (38). In addition, the Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guideline found bupropion to be more efficacious than placebo, based on many double-blind studies (level I) (27).

*Recommendations*

It is strongly recommended that bupropion is more efficacious than placebo in the treatment of depression.

**Key question 5-7.** Are serotonin antagonist and reuptake inhibitors (SARIs, trazodone) more efficacious than placebo in the treatment of depression?

*Evidence*

The APA and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines described trazodone as having a superior antidepressant effect over placebo (16, 27). Trazodone is still widely used, and shows better antidepressant effects compared to placebo (36, 39). Therefore, trazodone is recommended as more efficacious than placebo.

*Recommendations*

It is strongly recommended that trazodone is more efficacious than placebo in the treatment of depression.

**Key question 6.** Is there a difference among the efficacies of antidepressants?

**Key question 6-1.** When compared to other antidepressants, do TCAs have a different antidepressant efficacy?

*Evidence*

The NICE, APA, and BAP guidelines have described amitriptyline to be equal or slightly more effective than other antidepressants (SSRIs, SNRIs, MAOIs) (12, 13, 16). Especially in the case of inpatients, amitriptyline showed a slightly higher efficacy than

other TCAs or SSRIs (20, 40, 41). In addition, in melancholic depression and severe depression, its efficacy was superior to SSRIs (20). However, many side effects have been reported, and treatment can also be terminated due to the side effects.

*Recommendations*

It is strongly recommended that TCAs show a similar efficacy to other antidepressants.

**Key question 6-2.** When compared to other antidepressants, do MAOIs have a different antidepressive efficacy?

*Evidence*

The NICE, APA, BAP, Hong Kong, NSCCMHDA and University of Sydney CADE Clinic, TDMHMR in collaboration with Texas universities, and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have described MAOIs as having antidepressant efficacy equal to that of other antidepressants (12, 13, 15, 16, 24, 26). A meta-analysis on 12 reversible inhibitor of MAOA studies reported that moclobemide did not show a difference in efficacy compared to imipramine and clomipramine in admitted patients with severe depression or psychotic depression (42).

*Recommendations*

It is strongly recommended that MAOIs show equal efficacy to other antidepressants and moclobemide also shows equal efficacy.

**Key question 6-3.** When compared to other antidepressants, do SSRIs have a different antidepressive efficacy?

*Evidence*

The New Zealand guidelines group, NICE, CANMAT, APA, Hong Kong, and ACP guidelines described SSRIs as having similar antidepressant effects to other agents but better tolerability (12, 14, 16, 17, 24, 25). More than ten meta-analyses have reported SSRIs to be as effective as TCAs (18, 20, 43-45), and many studies have reported that there is not much evidence that other antidepressants are more effective than SSRIs (43, 46-50). Furthermore, the New Zealand guidelines group reported that escitalopram is superior to other SSRIs and venlafaxine (14, 49). SSRIs are also relatively safe when taken in large amounts, so they are recommended as a first-line treatment and also to patients with a risk of suicide. However, some studies have reported that SNRIs are superior to SSRIs in the remission of symptoms (51).

*Recommendations*

It is strongly recommended that SSRIs show similar efficacy to other antidepressants.

**Key question 6-4.** When compared to other antidepressants, do SNRIs have a different antidepressive efficacy?

*Evidence*

The NICE, CANMAT, APA, BAP, WFSBP, NSCCMHDA and University of Sydney CADE Clinic, Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology, and the Clinical Research Center for Depression guidelines have described venlafaxine and duloxetine to be equal or better in efficacy compared to other antidepressants (3, 12, 13, 15-17, 21, 27). The CANMAT guideline described venlafaxine to be superior to duloxetine, fluoxetine, and pooled SSRIs, and duloxetine to be superior to paroxetine and pooled SSRIs (17). The APA guideline reported venlafaxine and duloxetine to be as effective as SSRIs (16, 52, 53). A few studies have recommended SNRIs as more beneficial than SSRIs (51). However, there is evidence that patients taking venlafaxine discontinue the drug due to its side effects. In addition, whereas venlafaxine has proven to have an efficacy equal to TCA, there are not yet systematic studies comparing the efficacy of duloxetine and TCAs (51, 54). A meta-analysis comparing 105 studies on the difference in efficacy among antidepressants reported that no specific difference exists among the agents.

*Recommendations*

It is strongly recommended that SNRIs have a similar antidepressive efficacy compared to other antidepressants.

**Key question 6-5.** When compared to other antidepressants, do NaSSAs (mirtazapine) have a different antidepressive efficacy?

*Evidence*

The NICE, CANMAT, APA, BAP, ACP, WFSBP, Clinical Research Center for Depression, and the Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have described mirtazapine as having equal treatment efficacy to other antidepressants (3, 12, 13, 16, 17, 21, 25, 27). The NICE guideline described the possibility of reaching remission and decreasing depressive symptoms was greater compared to SSRIs, but no clinical significance was observed (12). However, mirtazapine was described to be less prone to early discontinuation compared to other antidepressants. The APA and Clinical Research Center for Depression guidelines described mirtazapine as having earlier onset of treatment efficacy compared to fluoxetine, paroxetine, and sertraline (3, 16, 36, 55, 56), but no significant difference was observed in the response rate. The APA guideline described mirtazapine as having equal efficacy to SSRIs (16, 57).

*Recommendations*

It is strongly recommended that mirtazapine has a similar anti-

depressive efficacy as other antidepressants.

**Key question 6-6.** When compared to other antidepressants, do NDRIs (bupropion) have a different antidepressive efficacy?

*Evidence*

The APA guideline described SSRIs to be more effective in patients diagnosed with depression and anxiety compared to bupropion (16, 58). However bupropion is effective for symptoms of fatigue and drowsiness and is FDA approved for cessation of smoking, and does not cause too much weight gain.

*Recommendations*

Bupropion may be weakly recommended to be effective as other antidepressants.

**Key question 6-7.** When compared to other antidepressants, do SARIs (trazodone) have a different antidepressive efficacy?

*Evidence*

The APA and Clinical Research Center for Depression guidelines reported trazodone to have an efficacy equal to that of TCAs and other antidepressants (3, 16). However, the CANMAT guideline described trazodone as not having a superior antidepressive efficacy compared to mirtazapine (17, 59), and the APA guideline described trazodone as showing inferior efficacy when treating severe depression or depression with severe psychomotor retardation compared to other antidepressants (16, 60, 61).

*Recommendations*

Trazodone may be weakly recommended to show similar antidepressive efficacy compared to other antidepressants.

**Key question 7.** When is the appropriate time to assess treatment efficacy if symptoms do not improve with antidepressant treatment?

*Evidence*

The NICE, CANMAT, and WFSBP guidelines have recommended 2-4 weeks as the appropriate time for assessment, and the BAP, Hong Kong, and Clinical Research Center for Depression guidelines have recommended at least 4 weeks before assessment (3, 12, 13, 17, 21, 24). The New Zealand guidelines group and TDMHMR in collaboration with Texas universities guidelines recommended 4-6 weeks (14, 26), the APA guideline recommended 4-8 weeks, and the ACP guideline recommended 6-8 weeks (16, 25).

*Recommendations*

When there is no improvement or only mild improvement of symptoms (25%), it is strongly recommended that treatment ef-

efficacy be assessed after 2-4 weeks. When there is a partial response, treatment should be continued for another 2-4 weeks before the assessment of treatment efficacy.

**Key question 8.** When there is an insufficient treatment response to first-line treatment, how should treatment be complemented?

#### *Evidence*

The New Zealand guidelines group, NICE, APA, BAP, WFSBP, Clinical Research Center for Depression, and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have recommended switching medication (3, 12-14, 16, 21, 27). The CANMAT, APA, BAP, Japan, TDMHMR in collaboration with Texas universities, WFSBP, Clinical Research Center for Depression, and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have recommended drug augmentation (3, 13, 16, 17, 21, 26, 27). The NICE, CANMAT, APA, BAP, TDMHMR in collaboration with Texas universities, WFSBP, Clinical Research Center for Depression, and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have recommended combination treatment with another antidepressant (3, 12, 13, 16, 17, 21, 26, 27). The New Zealand guidelines group, NICE, BAP, JCP, and Clinical Research Center for Depression guidelines have recommended an increase in dosage (3, 12-14).

#### *Recommendations*

When there is an insufficient treatment response, after reconsidering patient adherence, drug dosage, diagnosis, and treatment plan, an increase in dosage, drug augmentation, combination, switching medication, and concurrent psychotherapy are strongly recommended.

**Key question 9.** When first-line treatment does not result in treatment response, does increasing the dosage help achieve treatment response?

**Key question 9-1.** When treatment with TCAs does not result in treatment response, does increasing the dosage help achieve treatment response?

#### *Evidence*

The BAP and Clinical Research Center for Depression guidelines have indicated that increasing the dosage of TCAs is effective (3, 13). The BAP guideline reported that TCAs in high dosages (equivalent to 200-300 mg of imipramine) was more effective than standard dosages (13), and the Clinical Research Center for Depression guideline reported that TCAs showed better efficiency at higher blood levels, through studies reporting the

correlation of clinical efficiency and drug blood level measured by therapeutic drug monitoring (3).

#### *Recommendations*

It is strongly recommended that when there is no response to first-line treatment with TCAs, increasing the dose of TCAs may help treatment.

**Key question 9-2.** When treatment with MAOIs does not result in treatment response, does increasing the dosage help achieve treatment response?

#### *Evidence*

The Clinical Research Center for Depression guideline noted that increasing the dosage may be considered, but not enough evidence exists (3). Tranylcypromine, an irreversible MAOI, showed improved efficacy when increasing the dosage in the moderate- to high-dose range (90-180 mg/d), but increased efficacy was not observed in the moderate- to high-dose range according to some open label studies (62). Phenelzine was reported to show an increased treatment response with an increase in dosage in the moderate- to high-dose range (63).

#### *Recommendations*

It is strongly recommended that when there is no response to first-line treatment with MAOIs, increasing the dose may help treatment.

**Key question 9-3.** When treatment with SSRIs (including escitalopram) does not result in a treatment response, does increasing the dosage help achieve treatment response?

#### *Evidence*

The APA guideline reported that a higher dosage of SSRIs is more effective (16). MDD patients were assigned randomly to 0, 10, 20, 40, or 60 mg/day, and it was reported that the groups taking 10-20 mg showed more improvement than the placebo-treated group, but less improvement than the group taking 40-60 mg (64). However, the groups taking 20, 30, and 40 mg showed more side effects than the placebo group. The BAP guideline reported 20 mg of escitalopram as having better efficacy than 10 mg (13). On the other hand, the Clinical Research Center for Depression guideline indicated that increasing the dosage of fluoxetine and sertraline in treatment-resistant MDD patients did not significantly improve symptoms compared to maintaining the same dosage in such patients (3, 65, 66). Furthermore, a previous study reported that an increase in the dosage of paroxetine did not significantly improve symptoms (67).

#### *Recommendations*

It is strongly recommended that when there is no response to



first-line treatment with SSRIs, increasing the dose may improve outcomes.

**Key question 9-4.** When treatment with SNRIs (milnacipran, venlafaxine and duloxetine) does not result in treatment response, does increasing the dosage help achieve treatment response?

#### *Evidence*

The BAP guideline suggested that in treatment non-resistant patients, 225-375 mg of venlafaxine is more effective than 75 mg (68). The Clinical Research Center for Depression guideline also stated that at the highest doses, venlafaxine showed superior efficacy (3, 68, 69), and recommended that when patients do not show sufficient efficacy in the low dose range, dosages should be increased. However, studies comparing duloxetine in dosages of 40 mg and 80 mg, 30 mg and 60 mg, and 80 mg and 120 mg reported that the efficacy and receptivity did not have a statistically and clinically significant difference between the groups, although not many studies have been performed. Therefore, it was recommended that a dosage over 60 mg is not more effective.

#### *Recommendations*

It is strongly recommended that when there is no response to first-line treatment with SNRIs, increasing the dose may help treatment.

**Key question 10.** When first-line antidepressant treatment does not result in treatment response, does switching to another agent help achieve treatment response?

**Key question 10-1.** When there is no response to SSRIs, does switching to another agent help treatment?

#### *Evidence*

The CANMAT, BAP, WFSBP, and Clinical Research Center for Depression guidelines referenced 3 studies including a STAR\*D study, reporting that when SSRIs are not effective, switching to venlafaxine showed a 54% remission rate (3, 13, 17, 21, 70, 71). Further, the Clinical Research Center for Depression guideline referenced studies reporting it is effective to switch to TCAs when SSRIs are not effective. Also the medications preferred by psychiatrists in Korea were reported to be venlafaxine, mirtazapine, milnacipran, and bupropion (3). The CANMANT guideline also referenced a meta-analysis of 8 randomized controlled trials that reported when switching from SSRIs to other antidepressants, significant differences in treatment efficacy were not shown between antidepressants (17).

#### *Recommendations*

When patients do not respond to SSRIs, it is strongly recommen-

ded that switching to a non-SSRI antidepressant will help treatment.

**Key question 11.** How efficacious is the combination treatment of two antidepressants?

**Key question 11-1.** Is the combination treatment of TCAs and another antidepressant efficacious?

#### *Evidence*

The BAP guideline reported that the combination treatment of amitriptyline and moclobemide was more efficacious than amitriptyline therapy alone (13). The APA guideline reported that the combination treatment of TCAs and SSRIs shows a higher remission rate compared to therapy with either TCAs or SSRIs (16, 72).

#### *Recommendations*

There is strong evidence that when treatment response to first-line therapy is not sufficient, combination treatment with TCAs and another antidepressant is helpful.

**Key question 11-2.** Is the combination treatment of MAOIs and another antidepressant efficacious?

#### *Evidence*

The NICE and BAP guidelines reported that randomized control trials on the combination treatment of MAOIs and another antidepressant have been insufficient (12, 13). In particular, the number of controlled trials on the benefits or potential interactions of the combination treatment of TCAs and MAOIs in treatment-resistant depression is insufficient (73).

#### *Recommendations*

When treatment response to first-line therapy is insufficient, the combination treatment of MAOIs and another antidepressant is strongly not recommended.

**Key question 11-3.** Is the combination treatment of SSRIs and another antidepressant efficacious?

#### *Evidence*

The APA, BAP, NSCCMHDA and University of Sydney CADE Clinic, Clinical Research Center for Depression, and Hong Kong guidelines have recommended the combination treatment of SSRIs and another antidepressant (3, 13, 15, 16, 24). The efficacy of the combination treatment of mirtazapine and SSRIs was proven in a placebo-controlled study (74). The BAP guideline reported that the combination of reboxetine, bupropion, and TCAs with SSRIs are the most widely used (13). The Clinical Research Center for Depression guideline described combination

treatments of SSRIs and bupropion, while SSRIs and mirtazapine are the most preferred by psychiatrists in Korea (3). However, the combination of SSRIs and TCAs is still controversial. SSRIs hinder the metabolism of certain TCAs, and as a result, the blood pressure can rise, and toxicity and side effects can increase. In addition, the Clinical Research Center for Depression guideline noted that SSRIs and other antidepressants are used widely in combination in clinical settings, but most studies that are the basis of such use are open studies or case reports (3).

*Recommendations*

It is strongly recommended that when treatment response to first-line therapy is insufficient, the combination treatment of SSRIs and another antidepressant is helpful.

**Key question 11-4.** Is the combination treatment of SNRIs and another antidepressant efficacious?

*Evidence*

The APA guideline reported that the combination treatment of venlafaxine and mirtazapine will achieve a remission rate of 13.7% in patients that did not previously respond to 3 different medications (16, 75). On the other hand, the Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guideline reported that there is not much evidence on the effectiveness of the combination of venlafaxine and SSRIs (27). Further, when SSRIs that can suppress the metabolism of venlafaxine by CYP2D6 are taken in combination with venlafaxine, the blood level of venlafaxine can increase, and as a result, increased blood pressure, serotonin syndrome, and severe anticholinergic side effects may occur; hence, the combination of the agents must be performed with caution.

*Recommendations*

It is strongly recommended that when the treatment response to first-line therapy is insufficient, the combination treatment of SNRIs and another antidepressant is helpful.

**Key question 11-5.** Is the combination treatment of NASSAs (mirtazapine) and another antidepressant efficacious?

*Evidence*

The CANMAT, BAP, and Clinical Research Center for Depression guidelines described the combination treatment of mirtazapine or mianserin and other antidepressants (bupropion, venlafaxine, SSRIs, TCAs) as helpful (3, 13, 17). The CANMAT and APA guidelines have noted that the combination treatment of mirtazapine and SSRIs was shown to be superior in a placebo-controlled study (16, 17, 74).

*Recommendations*

It is strongly recommended that when the treatment response to first-line therapy is insufficient, the combination treatment of NaSSAs and another antidepressant is helpful.

**Key question 11-6.** Is the combination treatment of NDRIs (bupropion) and another antidepressant efficacious?

*Evidence*

The CANMAT, APA, BAP, WFSBP, and the Clinical Research Center for Depression guidelines all reported that the combination treatment of bupropion and SSRIs is efficacious (3, 13, 16, 17, 21). When unresponsive to citalopram, bupropion was shown to be superior to buspirone in effectiveness and tolerability when used in combination with citalopram (21). The combination treatment of SSRIs and bupropion was also shown to have superior efficacy to either agent used as monotherapy (76). The CANMAT guideline noted that many open-label studies and cohort studies have reported bupropion to be efficacious, but randomized controlled trials have not reported such efficacy (17, 77).

*Recommendations*

When treatment response to first-line therapy is insufficient, the combination treatment of NDRIs and another antidepressant may be weakly recommended to be helpful.

**Key question 11-7.** Is the combination treatment of SARIs (trazodone) and another antidepressant efficacious?

*Evidence*

The Clinical Research Center for Depression guideline reported that 100 mg trazodone combined with placebo, pindolol, or fluoxetine showed a response rate of 12.5% with placebo, 62.5% with pindolol, and 70% with fluoxetine (3, 78).

*Recommendations*

When treatment response to first-line therapy is insufficient, the combination treatment of SARIs and another antidepressant may be weakly recommended to be helpful.

**Key question 12.** How efficacious is adding an augmentation agent to an antidepressant?

**Key question 12-1.** Is adding lithium to an antidepressant helpful in the treatment of depression?

*Evidence*

Most of the guidelines supported augmentation therapy with lithium, and recommended lithium as the first-line treatment agent of a major depressive episode that does not respond to

classic antidepressant therapy (79-81).

#### *Recommendations*

When the treatment response to first-line therapy is insufficient, lithium augmentation therapy is strongly recommended to be helpful.

**Key question 12-2.** Is adding an anticonvulsant to an antidepressant helpful in the treatment of depression?

#### *Evidence*

The NICE, APA, BAP, Clinical Research Center for Depression, and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have suggested that evidence on the efficacy of anticonvulsant augmentation therapy is insufficient (3, 12, 13, 16). However, in those who did not respond to treatment previously, when a lamotrigine and fluoxetine augmentation group was compared to a lamotrigine monotherapy group, lamotrigine showed partial efficacy (82). Further, lithium and lamotrigine showed no significant difference in efficacy (53% vs 41%) (83).

#### *Recommendations*

When treatment response to first-line therapy is insufficient, although evidence on augmentation with anticonvulsants is insufficient, lamotrigine augmentation therapy may be weakly recommended to be helpful.

**Key question 12-3.** Is adding T3 to an antidepressant helpful in the treatment of depression?

#### *Evidence*

The NICE, CANMAT, APA, BAP, WFSBP, TDMHMR in collaboration with Texas universities, Clinical Research Center for Depression, and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have described T3 augmentation to be clinically efficacious in the treatment of depression (3, 12, 13, 15-17, 21, 26, 27).

#### *Recommendations*

When treatment response to first-line therapy is insufficient, T3 augmentation therapy may be weakly recommended to be helpful.

**Key question 12-4.** Is adding a benzodiazepine to an antidepressant helpful in the treatment of depression?

#### *Evidence*

The CANMAT, BAP, Hong Kong, NSCCMHDA and University of Sydney CADE Clinic, and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have recommended the short-term use of

benzodiazepines (13, 15, 17, 24). However, the NICE guideline described benzodiazepines to have insufficient evidence compared to placebo (12). The APA guideline reported that the use of antianxiety drugs and sedatives with SNRIs and SSRIs is not recommended for persistent anxiety and insomnia (16). The BAP and Hong Kong guidelines also recommended to be cautious about the risks of long-term use (13, 24).

#### *Recommendations*

A short period of benzodiazepine augmentation therapy is strongly recommended to be helpful.

**Key question 12-5.** Is adding atomoxetine to an antidepressant helpful in the treatment of depression?

#### *Evidence*

The NICE and BAP guidelines have reported that atomoxetine augmentation therapy does not result in a significant improvement in depressive symptoms, while monotherapy results in lower discontinuation rates due to side effects (12, 13).

#### *Recommendations*

When treatment response to first-line therapy is insufficient, atomoxetine augmentation therapy is strongly not recommended.

**Key question 12-6-1.** Is adding methylphenidate to an antidepressant helpful in the treatment of depression?

#### *Evidence*

The BAP, APA, and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have recommended methylphenidate augmentation therapy in the treatment of depression (13, 16, 27).

#### *Recommendations*

When treatment response to first-line therapy is insufficient, methylphenidate augmentation therapy is weakly recommended.

**Key question 12-6-2.** Is adding modafinil to an antidepressant helpful in the treatment of depression?

#### *Evidence*

The CANMAT, BAP, APA, and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have described modafinil as having a low possibility of causing dependency and cardiovascular side effects (13, 16, 17, 27). In addition, modafinil is described as being helpful with residual symptoms such as fatigue and sedation (84, 85). However, the CANMAT guideline has described two meta-analyses of placebo-controlled RCTs that have reported that, despite many advantages, overall negative results (17, 84, 85).

*Recommendations*

When treatment response to first-line therapy is insufficient, modafinil augmentation therapy is weakly recommended.

**Key question 13.** How long should antidepressant treatment be continued?

**Key question 13-1.** How long should antidepressant treatment be continued in continuation therapy?

*Evidence*

The New Zealand guidelines group, NICE, APA, TDMHMR in collaboration with Texas universities, and WFSBP guidelines have recommended that adult patients who have responded to antidepressant treatment should continue more than 6 months of antidepressant therapy in order to prevent relapse (12, 14, 16, 21, 26). The APA guideline recommended that patients who were successfully treated in the acute phase should continue treatment for 4-9 months (16). The TDMHMR in collaboration with Texas universities guideline recommended continuing therapy for 6-9 months after remission (26). The WFSBP guideline recommended continuing therapy for more than 9 months, considering the patient's psychiatric history, and if there are persisting symptoms, treatment should be continued until all symptoms resolve (21).

*Recommendations*

It is strongly recommended that treatment be continued for at least 6 months after remission.

**Key question 13-2.** How long should antidepressant treatment be continued in maintenance therapy?

*Evidence*

The Hong Kong, NSCCMHDA and University of Sydney CADE Clinic, WFSBP, and Clinical Research Center for Depression guidelines have recommended that patients with recurrent MDD continue treatment for 3 yr (3, 15, 21, 24). The APA guideline has recommended maintenance therapy for patients who have experienced 3 or more depressive episodes (16), while the Hong Kong and NSCCMHDA and University of Sydney CADE Clinic guidelines have recommended maintenance therapy of 3-6 months or 1 yr after the first depressive episode (15, 24).

*Recommendations*

It is strongly recommended that maintenance therapy be continued for at least 3 yr for recurrent MDD.

**Key question 14.** What are the withdrawal symptoms of antidepressants and the management of such symptoms?

*Evidence*

The NICE, APA, ACP, and NSCCMHDA and University of Sydney CADE Clinic guidelines have described the withdrawal symptoms of antidepressants to include an increase in mood fluctuation (for example, hypersensitivity), gastrointestinal symptoms (nausea), neuromotor abnormalities (ataxia), vasomotor abnormalities (sweating), neurosensory abnormalities (sensory abnormalities), insomnia and other neurological problems (12, 15, 16, 25). The NSCCMHDA and University of Sydney CADE Clinic guideline described general withdrawal symptoms of SSRIs as flu-like symptoms, a shock-like sensation, dizziness, dreaming excessively, insomnia, and tearing. The general withdrawal symptoms of TCAs were described as flu-like symptoms and insomnia (15). The APA and ACP guidelines reported that paroxetine may have a long-term discontinuation syndrome, and venlafaxine may have similar symptoms as well (16, 25). Most of the guidelines have recommended a slow tapering down of antidepressants or retaking the previous antidepressant or switching to an antidepressant that has a long half-life.

*Recommendations*

It is strongly recommended that antidepressants be tapered slowly as to prevent withdrawal symptoms. When withdrawal symptoms appear, it is strongly recommended that the previous medication be taken again or that an antidepressant in the same line with a longer half-life be administered.

**Key question 15.** Do antidepressants influence the suicide of MDD patients?

*Evidence*

The CANMAT, APA, BAP, Hong Kong, and WFSBP guidelines have reported that there is no clear evidence on whether antidepressants increase suicide-related behaviors in adults (13, 16, 17, 21, 24). However, suicidal risks may increase in patients under 30 yr old who are receiving initial treatment, and the APA guideline has quoted the results of a meta-analysis reporting that suicidal ideation and rates were statistically 1.5-2.5 times higher in patients 25 yr old and under, compared to control groups (16). On the other hand, the ACP guideline quoted a meta-analysis reporting no evidence that antidepressants increase suicide risks, but the risk of suicide attempts that are not fatal may increase (25, 86).

*Recommendations*

Although the evidence that antidepressants increase the suicide rate is insufficient, it is strongly recommended that clinicians show caution in light of the suicide risk of patients 25 yr old and under.

**Table 2.** Recommendations made in the 'Evidence-Based, Pharmacological Treatment Guideline for Depression in Korea, Revised Edition'

Treatment	Strongly recommend	Weakly recommend	Weakly not recommend	Strongly not recommend
Initiation of treatment				
KQ1. First-line treatment agent among antidepressants	<ul style="list-style-type: none"> <li>· SSRIs</li> <li>· SNRIs</li> <li>· NDRIs</li> <li>· NaSSAs</li> </ul>	· TCAs		
KQ3. Factor that influences the choice of antidepressants	<ul style="list-style-type: none"> <li>· Potential side effects</li> <li>· Patient history of side effects</li> <li>· Drug interaction</li> <li>· Previous treatment response</li> <li>· Preference and acceptability of the patient</li> <li>· Cost of treatment</li> <li>· Co-existing disease</li> </ul>			
KQ2. Antidepressant for patients with low tolerance		· SSRIs		
Treatment efficacy				
KQ4-1. Antidepressant effective in atypical depression		· SSRIs		
KQ4-2. Antidepressant effective in psychotic depression	· Augmentation of antidepressants with antipsychotic medication			
KQ4-3. Antidepressant effective in seasonal depression		· SSRIs · Bupropion		
KQ5. Antidepressant more effective than placebo	<ul style="list-style-type: none"> <li>· TCAs</li> <li>· MAOIs</li> <li>· SSRIs (including escitalopram)</li> <li>· SNRIs (duloxetine and venlafaxine)</li> <li>· NaSSAs (mirtazapine)</li> <li>· NDRIs (bupropion)</li> <li>· SARIs (trazodone)</li> </ul>			
KQ6. Antidepressant that shows similar efficacy to other antidepressants	<ul style="list-style-type: none"> <li>· TCAs</li> <li>· MAOIs, moclobemide</li> <li>· SSRIs (including escitalopram)</li> <li>· SNRIs</li> <li>· NaSSA (mirtazapine)</li> </ul>	<ul style="list-style-type: none"> <li>· NDRI (bupropion)</li> <li>· SARI (trazodone)</li> </ul>		
Insufficient improvement of symptoms				
KQ7. Appropriate time to assess treatment efficacy when symptoms do not improve with antidepressant treatment	<ul style="list-style-type: none"> <li>· Assess treatment efficacy after 2-4 weeks when there is no improvement or only mild improvement of symptoms (25%)</li> <li>· Treatment should be further continued for another 2-4 weeks before the assessment of treatment efficacy, when there is partial response</li> </ul>			
Insufficient treatment response to first-line therapy				
KQ8. How to complement treatment	<ul style="list-style-type: none"> <li>· Increase drug dosage</li> <li>· Augmentation therapy</li> <li>· Combination therapy</li> <li>· Switching of medication</li> <li>· Concurrent psychotherapy</li> </ul>			
KQ11. Antidepressant that is helpful when combined with another antidepressant	<ul style="list-style-type: none"> <li>· TCAs</li> <li>· SSRIs</li> <li>· SNRIs</li> <li>· NaSSAs (mirtazapine)</li> </ul>	<ul style="list-style-type: none"> <li>· NDRIs (bupropion)</li> <li>· SARIs (trazodone)</li> </ul>		· MAOIs
KQ12. Augmentation agent of antidepressant	<ul style="list-style-type: none"> <li>· Lithium</li> <li>· Benzodiazepine (short period)</li> </ul>	<ul style="list-style-type: none"> <li>· Lamotrigine</li> <li>· T3</li> <li>· Methylphenidate</li> <li>· Modafinil</li> </ul>		· Atomoxetine
No response to first-line therapy				
KQ9. Antidepressant that helps treatment by increasing the dosage	<ul style="list-style-type: none"> <li>· TCAs</li> <li>· MAOIs</li> <li>· SSRIs</li> <li>· SNRIs (milnacipran, venlafaxine, duloxetine)</li> </ul>			
KQ10. Antidepressant that helps treatment when switching to another agent	· SSRIs (switch to a non-SSRI antidepressant)			
Continuation of treatment				
KQ13-1. Continuation therapy	· Continue treatment for more than 6 months after remission			
KQ13-2. Maintenance therapy	· Continue maintenance therapy for more than 3 years for recurrent MDD			
Withdrawal symptoms of antidepressants				
KQ14. Management of withdrawal symptoms of antidepressant	<ul style="list-style-type: none"> <li>· Taper antidepressant slowly as to prevent withdrawal symptoms</li> <li>· Retake the previous medication or administer an antidepressant of the same line with a longer half-life when withdrawal symptoms appear</li> </ul>			
Influence of antidepressants on suicide				
KQ15. Influence of antidepressants on suicide of MDD patients	· Take caution in the suicide risk of patients 25 years old and under			
Side effects of antidepressants				
KQ16-1. Antidepressant to prescribe when patients complain of sexual side effects	· Bupropion	· Mirtazapine		

TCAs, Tricyclic Antidepressants; MAOIs, Monoamine Oxidase Inhibitors; SSRIs, Selective Serotonin Reuptake Inhibitors; SNRIs, Serotonin and Norepinephrine Reuptake Inhibitors; NaSSAs, Norepinephrine and Specific Serotonergic Antidepressants; NDRIs, Norepinephrine and Dopamine Reuptake Inhibitors; SARIs, Serotonin Antagonist and Reuptake Inhibitors; MDD, Major depressive disorder.

**Key question 16.** What are the serious side effects of antidepressants?

**Key question 16-1.** Are there differences in sexual side effects among different antidepressant treatments?

#### Evidence

The NICE, CANMAT, APA, BAP, ACP, TDMHMR in collaboration with Texas universities, Clinical Research Center for Depression, and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have reported that SSRIs have higher sexual side effects, and among the SSRIs, paroxetine has a higher rate of sexual dysfunction compared to other antidepressants (3, 12, 13, 16, 17, 25-27). The CANMAT, ACP, TDMHMR in collaboration with Texas universities, Clinical Research Center for Depression, and Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology guidelines have described bupropion as having a similar rate of sexual side effects to placebo (3, 17, 25-27). It was also recommended to switch to bupropion when sexual side effects arise from other antidepressants (87). Furthermore, mirtazapine was reported to cause sexual side effects at a similarly low rate to bupropion. The ACP guideline described paroxetine as causing sexual side effects; however, the exact rate has not yet been reported (25).

#### Recommendations

It is strongly recommended that bupropion be prescribed to patients who complain of sexual side effects, and mirtazapine can also be weakly recommended.

## DISCUSSION

A clinical practice guideline can be defined as a systematic description that helps clinicians and patients choose their health management program in a specific clinical situation. The present guideline was developed to reduce the discrepancies in clinical treatment, inappropriate levels of treatment, and treatment costs by improving the quality of treatment in Korea. Not only the USA and UK, but also Canada, New Zealand, and Singapore are developing their own evidence-based guidelines. Guidelines that have been developed by evidence-based methods are becoming the mainstream treatment modality worldwide for the following reasons: First, given the huge amount of published research these days, no one individual can keep up with the rate of development of medical knowledge; second, treatment recommendations may be contradictory among experts, and if clinical practice is only based on the judgment of the practitioner, different recommendations may be made in the same clinical situation.

In summary, our evidence-based treatment guideline has

made certain recommendations considered appropriate to the current clinical situation of Korea (Table 2). The revised edition of the treatment guideline is considered to comprise new clinical information, and to reflect the current clinical situation of Korea, when compared to the previous version. Furthermore, the Evidence-based, Non-pharmacological Treatment Guideline for Depression in Korea (4) has also been developed, which strengthens the holistic approach of the guidelines to the treatment of depression when used together. The next step for the treatment guideline development team to take may be harmonizing the pharmacological and non-pharmacological treatment guidelines to a single comprehensive guideline, in order to complete the holistic approach to treating depression. Until further development of specific methodologies for the pharmacological treatment of depression is achieved in Korea, we recommend the wide distribution of the Evidence-based Pharmacological Treatment Guideline for Depression in Korea, Revised Edition, so that it is available to all clinical practitioners. The guideline is considered to be helpful when selecting the appropriate pharmacological treatment for MDD patients in Korea.

## DISCLOSURE

The authors have no conflicts of interest to disclose.

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## REFERENCES

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. *Global burden of disease and risk factors*. Washington, D.C.: World Bank, 2006.

2. Lee MS, Cha JH, Chung SK, Kim KS, Kasper S; the Executive Committee for the Korean Medication Algorithm Project for Major Depressive Disorder. *The development of the Korean medication algorithm for major depressive disorder. Psychiatry Invest* 2005; 2: 60-9.
3. Clinical Research Center for Depression. *Evidence-based Korean pharmacological treatment guideline for depression. Seoul: ML Communication, 2008.*
4. Park SC, Oh HS, Oh DH, Jung SA, Na KS, Lee HY, Kang RH, Choi YK, Lee MS, Park YC. *Evidence-based, non-pharmacological treatment guideline for depression in Korea. J Korean Med Sci* 2014; 29: 12-22.
5. Clinical Research Center for Depression. *Evidence-based Korean pharmacological treatment guideline for depression, revised edition. Seoul: ML Communication, 2012.*
6. Park SC, Sung SH, Han KM, Won ES, Lee HY, Paik JW, Jeon HJ, Lee MS, Shim SH, Ko YH, et al. *Evidence-based Korean pharmacological treatment guideline for depression, revised edition (I): initial choice of antidepressant treatment. J Korean Neuropsychiatr Assoc* 2013; 52: 253-62.
7. Sung SH, Park SC, Han KM, Won ES, Lee HY, Koo JW, Paik JW, Lee KM, Jeon HJ, Lee MS, et al. *Evidence-based Korean pharmacological treatment guideline for depression, revised edition (II): antidepressant efficacy compared with placebo, difference in efficacy of antidepressants, and appropriate time of efficacy judgment in antidepressant therapy. J Korean Neuropsychiatr Assoc* 2013; 52: 372-85.
8. Han KM, Park SC, Won ES, Sung SH, Lee H, Koo JW, Lee K, Lee HY, Paik JW, Jeon HJ, et al. *Evidence-based Korean pharmacological treatment guideline for depression, revised edition (III): dose increment, switching, combination, and augmentation strategy in antidepressant therapy. J Korean Neuropsychiatr Assoc* 2013; 52: 386-401.
9. Huang X, Lin J, Demner-Fushman D. *Evaluation of PICO as a knowledge representation for clinical questions. AMIA Annu Symp Proc* 2006; 2006: 359-63.
10. Kim SY KN, Shin SS, Kim DW, Ji SM, Lee SJ. *ADAPTE: manual for guideline adaptation version 1.0. Seoul: National Clinical Research Coordination Center, 2009.*
11. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ; GRADE Working Group. *Going from evidence to recommendations. BMJ* 2008; 336: 1049-51.
12. National Institute for Health and Clinical Excellence (NICE). *Depression: the treatment and management of depression in adults (updated edition). Leicester: British Psychological Society, 2010.*
13. Anderson IM, Ferrier IN, Baldwin RC, Cowen PJ, Howard L, Lewis G, Matthews K, McAllister-Williams RH, Peveler RC, Scott J, 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: 343-96.
14. The New Zealand guidelines group. *Identification of common mental disorders and management of depression in primary care. New Zealand: Ministry of Health, 2008.*
15. Malhi GS, Adams D, Porter R, Wignall A, Lampe L, O'Connor N, Paton M, Newton LA, Walter G, Taylor A, et al. *Clinical practice recommendations for depression. Acta Psychiatr Scand Suppl* 2009; (439): 8-26.
16. Practice guideline for the treatment of patients with major depressive disorder (revision): American Psychiatric Association. *Am J Psychiatry* 2000; 157: 1-45.
17. Lam RW, Kennedy SH, Grigoriadis S, McIntyre RS, Milev R, Ramasubbu R, Parikh SV, Patten SB, Ravindran AV; Canadian Network for Mood and Anxiety Treatments (CANMAT). *Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults: III. pharmacotherapy. J Affect Disord* 2009; 117: S26-43.
18. Montgomery SA. *A meta-analysis of the efficacy and tolerability of paroxetine versus tricyclic antidepressants in the treatment of major depression. Int Clin Psychopharmacol* 2001; 16: 169-78.
19. Puech A, Montgomery SA, Prost JE, Solles A, Briley M. *Milnacipran, a new serotonin and noradrenaline reuptake inhibitor: an overview of its antidepressant activity and clinical tolerability. Int Clin Psychopharmacol* 1997; 12: 99-108.
20. Anderson IM. *Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord* 2000; 58: 19-36.
21. Bauer M, Bschor T, Pfennig A, Whybrow PC, Angst J, Versiani M, Möller HJ; WFSBP Task Force on Unipolar Depressive Disorders. *World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for biological treatment of unipolar depressive disorders in primary care. World J Biol Psychiatry* 2007; 8: 67-104.
22. Simon GE, VonKorff M, Heiligenstein JH, Revicki DA, Grothaus L, Katon W, Wagner EH. *Initial antidepressant choice in primary care: effectiveness and cost of fluoxetine vs tricyclic antidepressants. JAMA* 1996; 275: 1897-902.
23. Vaswani M, Linda FK, Ramesh S. *Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. Prog Neuropsychopharmacol Biol Psychiatry* 2003; 27: 85-102.
24. Professional Development & Quality Assurance prepared by a group of family physicians. *Guideline on Management of Depression in Primary Care. Hong Kong, 2005.*
25. Qaseem A, Snow V, Denberg TD, Forciea MA, Owens DK; Clinical Efficacy Assessment Subcommittee of American College of Physicians. *Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med* 2008; 149: 725-33.
26. Texas Department of Mental Health and Mental Retardation (TDMHMR) in collaboration with Texas universities. *Texas medication algorithm project procedural manual - major depressive disorder algorithms. Texas Department of State Health Services, 2008.*
27. Korean Society for Depressive and Bipolar Disorders and Korean College of Neuropsychopharmacology. *Korean medication algorithm project for depressive disorder. Korean Neuropsychiatr Assoc, 2008.*
28. Moscovitch A, Blashko CA, Eagles JM, Darcourt G, Thompson C, Kasper S, Lane RM; International Collaborative Group on Sertraline in the Treatment of Outpatients with Seasonal Affective Disorders. *A placebo-controlled study of sertraline in the treatment of outpatients with seasonal affective disorder. Psychopharmacology (Berl)* 2004; 171: 390-7.
29. Lam RW, Gorman CP, Michalon M, Steiner M, Levitt AJ, Corral MR, Watson GD, Morehouse RL, Tam W, Joffe RT. *Multicenter, placebo-controlled study of fluoxetine in seasonal affective disorder. Am J Psychiatry* 1995; 152: 1765-70.
30. Ruhrmann S, Kasper S, Hawellek B, Martinez B, Höflich G, Nickelsen T, Möller HJ. *Effects of fluoxetine versus bright light in the treatment of seasonal affective disorder. Psychol Med* 1998; 28: 923-33.
31. Bodkin JA, Amsterdam JD. *Transdermal selegiline in major depression:*

- a double-blind, placebo-controlled, parallel-group study in outpatients. *Am J Psychiatry* 2002; 159: 1869-75.
32. Amsterdam JD. A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. *J Clin Psychiatry* 2003; 64: 208-14.
  33. Feiger AD, Rickels K, Rynn MA, Zimbroff DL, Robinson DS. Selegiline transdermal system for the treatment of major depressive disorder: an 8-week, double-blind, placebo-controlled, flexible-dose titration trial. *J Clin Psychiatry* 2006; 67: 1354-61.
  34. Khan A, Khan SR, Leventhal RM, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: a replication analysis of the Food and Drug Administration Database. *Int J Neuropsychopharmacol* 2001; 4: 113-8.
  35. Bech P, Cialdella P, Haugh MC, Birkett MA, Hours A, Boissel JP, Tollefson GD. Meta-analysis of randomised controlled trials of fluoxetine v. placebo and tricyclic antidepressants in the short-term treatment of major depression. *Br J Psychiatry* 2000; 176: 421-8.
  36. Bech P. Meta-analysis of placebo-controlled trials with mirtazapine using the core items of the Hamilton Depression Scale as evidence of a pure antidepressive effect in the short-term treatment of major depression. *Int J Neuropsychopharmacol* 2001; 4: 337-45.
  37. Modell JG, Rosenthal NE, Harriett AE, Krishen A, Asgharian A, Foster VJ, Metz A, Rockett CB, Wightman DS. Seasonal affective disorder and its prevention by anticipatory treatment with bupropion XL. *Biol Psychiatry* 2005; 58: 658-67.
  38. Fava M, Rush AJ, Thase ME, Clayton A, Stahl SM, Pradko JF, Johnston JA. 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim Care Companion J Clin Psychiatry* 2005; 7: 106-13.
  39. Pitts WM, Fann WE, Halaris AE, Dressler DM, Sajadi C, Snyder S, Ilaria RL. Bupropion in depression: a tri-center placebo-controlled study. *J Clin Psychiatry* 1983; 44: 95-100.
  40. Barbui C, Hotopf M. Amitriptyline v. the rest: still the leading antidepressant after 40 years of randomised controlled trials. *Br J Psychiatry* 2001; 178: 129-44.
  41. Guaiana G, Barbui C, Hotopf M. Amitriptyline versus other types of pharmacotherapy for depression. *Cochrane Database Syst Rev* 2003; (2): CD004186.
  42. Angst J, Amrein R, Stahl M. Moclobemide and tricyclic antidepressants in severe depression: meta-analysis and prospective studies. *J Clin Psychopharmacol* 1995; 15: 165-235.
  43. Cipriani A, Brambilla P, Furukawa T, Geddes J, Gregis M, Hotopf M, Malvini L, Barbui C. Fluoxetine versus other types of pharmacotherapy for depression. *Cochrane Database Syst Rev* 2005; (4): CD004185.
  44. MacGillivray S, Arroll B, Hatcher S, Ogston S, Reid I, Sullivan F, Williams B, Crombie I. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. *BMJ* 2003; 326: 1014.
  45. Arroll B, Elley CR, Fishman T, Goodyear-Smith FA, Kenealy T, Blashki G, Kerse N, Macgillivray S. Antidepressants versus placebo for depression in primary care. *Cochrane Database Syst Rev* 2009; (3): CD007954.
  46. Panzer MJ. Are SSRIs really more effective for anxious depression? *Ann Clin Psychiatry* 2005; 17: 23-9.
  47. Geddes JR, Freemantle N, Mason J, Eccles MP, Boynton J. SSRIs versus other antidepressants for depressive disorder. *Cochrane Database Syst Rev* 2000; (2): CD001851.
  48. Barbui C, Hotopf M, Freemantle N, Boynton J, Churchill R, Eccles MP, Geddes JR, Hardy R, Lewis G, Mason JM. Selective serotonin reuptake inhibitors versus tricyclic and heterocyclic antidepressants: comparison of drug adherence. *Cochrane Database Syst Rev* 2000; (4): CD002791.
  49. Kennedy SH, Andersen HF, Lam RW. Efficacy of escitalopram in the treatment of major depressive disorder compared with conventional selective serotonin reuptake inhibitors and venlafaxine XR: a meta-analysis. *J Psychiatry Neurosci* 2006; 31: 122-31.
  50. Gartlehner G, Gaynes BN, Hansen RA, Thieda P, DeVeugh-Geiss A, Krebs EE, Moore CG, Morgan L, Lohr KN. Comparative benefits and harms of second-generation antidepressants: background paper for the American College of Physicians. *Ann Intern Med* 2008; 149: 734-50.
  51. Bauer M, Tharmanathan P, Volz HP, Moeller HJ, Freemantle N. The effect of venlafaxine compared with other antidepressants and placebo in the treatment of major depression: a meta-analysis. *Eur Arch Psychiatry Clin Neurosci* 2009; 259: 172-85.
  52. Perahia DG, Pritchett YL, Kajdasz DK, Bauer M, Jain R, Russell JM, Walker DJ, Spencer KA, Froud DM, Raskin J, et al. A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. *J Psychiatr Res* 2008; 42: 22-34.
  53. Thase ME, Pritchett YL, Ossanna MJ, Swindle RW, Xu J, Detke MJ. Efficacy of duloxetine and selective serotonin reuptake inhibitors: comparisons as assessed by remission rates in patients with major depressive disorder. *J Clin Psychopharmacol* 2007; 27: 672-6.
  54. Smith D, Dempster C, Glanville J, Freemantle N, Anderson I. Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. *Br J Psychiatry* 2002; 180: 396-404.
  55. Schatzberg AF, Kremer C, Rodrigues HE, Murphy GM Jr; Mirtazapine vs. Paroxetine Study Group. Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am J Geriatr Psychiatry* 2002; 10: 541-50.
  56. Benkert O, Szegedi A, Kohonen R. Mirtazapine compared with paroxetine in major depression. *J Clin Psychiatry* 2000; 61: 656-63.
  57. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. *Biol Psychiatry* 2008; 63: 699-704.
  58. Papakostas GI, Stahl SM, Krishen A, Seifert CA, Tucker VL, Goodale EP, Fava M. Efficacy of bupropion and the selective serotonin reuptake inhibitors in the treatment of major depressive disorder with high levels of anxiety (anxious depression): a pooled analysis of 10 studies. *J Clin Psychiatry* 2008; 69: 1287-92.
  59. Montgomery SA, Baldwin DS, Blier P, Fineberg NA, Kasper S, Lader M, Lam RW, Lépine JP, Möller HJ, Nutt DJ, et al. Which antidepressants have demonstrated superior efficacy? a review of the evidence. *Int Clin Psychopharmacol* 2007; 22: 323-9.
  60. Bollini P, Pampallona S, Tibaldi G, Kupelnick B, Munizza C. Effectiveness of antidepressants: meta-analysis of dose-effect relationships in randomised clinical trials. *Br J Psychiatry* 1999; 174: 297-303.
  61. Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *J Affect Disord* 1999; 56: 171-81.
  62. Adli M, Baethge C, Heinz A, Langlitz N, Bauer M. Is dose escalation of



- antidepressants a rational strategy after a medium-dose treatment has failed? a systematic review. Eur Arch Psychiatry Clin Neurosci* 2005; 255: 387-400.
63. Amsterdam JD, Berwisch NJ. *High dose tranylcypromine therapy for refractory depression. Pharmacopsychiatry* 1989; 22: 21-5.
  64. Gagiano CA, Müller FG, Berk M, Joubert PM, Brown RG, Schall R. *Moclobemide twice daily in the treatment of major depressive episode: a double-blind, multicenter comparison with different three times daily dosage schedules. J Clin Psychopharmacol* 1995; 15: 4S-9S.
  65. Burke WJ, Gergel I, Bose A. *Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. J Clin Psychiatry* 2002; 63: 331-6.
  66. Bech P, Tanghøj P, Andersen HF, Overø K. *Citalopram dose-response revisited using an alternative psychometric approach to evaluate clinical effects of four fixed citalopram doses compared to placebo in patients with major depression. Psychopharmacology (Berl)* 2002; 163: 20-5.
  67. Schweizer E, Rickels K, Amsterdam JD, Fox I, Puzzuoli G, Weise C. *What constitutes an adequate antidepressant trial for fluoxetine? J Clin Psychiatry* 1990; 51: 8-11.
  68. Rudolph RL, Fabre LF, Feighner JP, Rickels K, Entsuah R, Derivan AT. *A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. J Clin Psychiatry* 1998; 59: 116-22.
  69. Schweizer E, Weise C, Clary C, Fox I, Rickels K. *Placebo-controlled trial of venlafaxine for the treatment of major depression. J Clin Psychopharmacol* 1991; 11: 233-6.
  70. Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, Ritz L, Biggs MM, Warden D, Luther JF, et al. *Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med* 2006; 354: 1231-42.
  71. Ruhé HG, Huyser J, Swinkels JA, Schene AH. *Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review. J Clin Psychiatry* 2006; 67: 1836-55.
  72. Nelson JC, Mazure CM, Jatlow PI, Bowers MB Jr, Price LH. *Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. Biol Psychiatry* 2004; 55: 296-300.
  73. Lader M. *Combined use of tricyclic antidepressants and monoamine oxidase inhibitors. J Clin Psychiatry* 1983; 44: 20-4.
  74. Carpenter LL, Yasmin S, Price LH. *A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biol Psychiatry* 2002; 51: 183-8.
  75. McGrath PJ, Stewart JW, Fava M, Trivedi MH, Wisniewski SR, Nierenberg AA, Thase ME, Davis L, Biggs MM, Shores-Wilson K, et al. *Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR\*D report. Am J Psychiatry* 2006; 163: 1531-41.
  76. Lam RW, Hossie H, Solomons K, Yatham LN. *Citalopram and bupropion-SR: combining versus switching in patients with treatment-resistant depression. J Clin Psychiatry* 2004; 65: 337-40.
  77. Dodd S, Horgan D, Malhi GS, Berk M. *To combine or not to combine? a literature review of antidepressant combination therapy. J Affect Disord* 2005; 89: 1-11.
  78. Maes M, Vandoolaeghe E, Desnyder R. *Efficacy of treatment with trazodone in combination with pindolol or fluoxetine in major depression. J Affect Disord* 1996; 41: 201-10.
  79. Nelson JC. *Overcoming treatment resistance in depression. J Clin Psychiatry* 1998; 59: 13-9.
  80. Nemeroff CB. *Augmentation strategies in patients with refractory depression. Depress Anxiety* 1996; 4: 169-81.
  81. Shelton RC. *Treatment options for refractory depression. J Clin Psychiatry* 1999; 60: 57-61.
  82. Barbosa L, Berk M, Vorster M. *A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. J Clin Psychiatry* 2003; 64: 403-7.
  83. Schindler F, Angheliescu IG. *Lithium versus lamotrigine augmentation in treatment resistant unipolar depression: a randomized, open-label study. Int Clin Psychopharmacol* 2007; 22: 179-82.
  84. Fava M, Thase ME, DeBattista C, Doghramji K, Arora S, Hughes RJ. *Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. Ann Clin Psychiatry* 2007; 19: 153-9.
  85. DeBattista C, Doghramji K, Menza MA, Rosenthal MH, Fieve RR; Modafinil in Depression Study Group. *Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. J Clin Psychiatry* 2003; 64: 1057-64.
  86. Gunnell D, Saperia J, Ashby D. *Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. BMJ* 2005; 330: 385.
  87. Taylor MJ, Rudkin L, Hawton K. *Strategies for managing antidepressant-induced sexual dysfunction: systematic review of randomised controlled trials. J Affect Disord* 2005; 88: 241-54.