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Research paper

Pharmacological management of depression: Japanese expert consensus

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ABSTRACT

Background: Clinically relevant issues in the real-world treatment of depression have not always been captured by conventional treatment guidelines.
Methods: Certified psychiatrists of the Japanese Society of Clinical Neuropsychopharmacology were asked to evaluate treatment options regarding 23 clinical situations in the treatment of depression using a 9-point Likert scale (1 = "disagree" and 9 = "agree"). According to the responses of 114 experts, the options were categorized into first-, second-, and third-line treatments.
Results: First-line antidepressants varied depending on predominant symptoms: escitalopram (mean ± standard deviation score, 7.8 ± 1.7) and sertraline (7.3 ± 1.7) were likely selected for anxiety; duloxetine (7.6 ± 1.9) and venlafaxine (7.2 ± 2.1) for loss of interest; mirtazapine for insomnia (8.2 ± 1.6), loss of appetite (7.9 ± 1.9), agitation and severe irritation (7.4 ± 2.0), and suicidal ideation (7.5 ± 1.9). While first-line treatment was switched to either an SNRI (7.7 ± 1.9) or mirtazapine (7.4 ± 2.0) in the case of non-response to an SSRI, switching to mirtazapine (7.1 ± 2.2) was recommended in the case of non-response to an SNRI, and vice versa (switching to an SNRI (7.0 ± 2.0) in the case of non-response to mirtazapine). Augmentation with aripiprazole was considered the first-line treatment for partial response to an SSRI (7.1 ± 2.3) or SNRI (7.0 ± 2.5).
Limitations: The evidence level of expert consensus is considered low. All included experts were Japanese.
Conclusions: Recommendations made by experts in the field are useful and can supplement guidelines and informed decision making in real-world clinical practice. We suggest that pharmacological strategies for depression be flexible and that each patient's situational needs as well as the pharmacotherapeutic profile of medications be considered.

Abbreviations: CI, confidence interval; JSCNP, japanese society of clinical neuropsychopharmacology; MDD, major depressive disorder; PRN, "pro re nata"; SD, standard deviation; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TeCA, tetracyclic antidepressant

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1. Introduction

Treatment guidelines for major depressive disorder (MDD) are generally based on solid evidence that mainly stems from randomized controlled trials. However, due to this evidence-based approach, the guidelines are sometimes unable to provide clear treatment recommendations for issues that are clinically relevant but failed to be addressed in clinical studies. For example, conventional treatment guidelines recommend the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin and noradrenaline reuptake inhibitors (SNRIs) for the initial treatment of depression, but they do not go on to address specific choices of antidepressants depending on clinical symptoms (Bayes and Parker, 2018). Moreover, detailed recommendations on when and how to discontinue antidepressants are not available.

Consensus amongst experts in the field is considered useful to fill the gap regarding clinically challenging issues that have not been addressed with a high level of evidence in the literature. Several treatment guidelines have been widely used; however, there has been no newly published guideline with respect to depression management in the past few years (American Psychiatric Association, 2010; Bauer et al., 2013, 2015; Brandon Suehs et al., 2008; Cleare et al., 2015; Kennedy et al., 2016; Malhi et al., 2015; National Collaborating Centre for Mental Health (UK), 2010; National Institute for Health and Care Excellence, 2009a; World Health Organization, 2009).

The Japanese Society of Clinical Neuropsychopharmacology (JSCNP) is an academic society dedicated to clinical psychopharmacology to improve the pharmacological treatment of psychiatric disorders. This society has a board certification system in which psychiatrists in the society are certified as specialists in the field of clinical psychopharmacology based on their academic activities as well as scores on written examinations regarding professional expertise. A total of 277 psychiatrists were certified as of August 2019. Here, to reflect recommendations by the board-certified experts of the JSCNP, we developed an expert consensus guideline on clinically relevant issues regarding the treatment of depression that had not been adequately represented in the conventional treatment guidelines. Our main focus was threefold: Which antidepressants should be chosen as first-line treatments? What should be done when the initial choice results in little or no response? When should antidepressants be discontinued? All three questions remain controversial in the literature.

2. Methods

2.1. Study design

This survey was conducted from March 20, 2019, to April 25, 2019. After a thorough assessment of currently available treatment guidelines for depression, the Medical Education Panel of the JSCNP, which consisted of 13 experts, identified 23 clinical situations that had not been clearly addressed in the literature. For each clinical situation, treatment options were proposed. The certified psychiatrists were asked to evaluate the proposed treatment options using a 9-point Likert scale (1 = "disagree" and 9 = "agree"). These clinical situations and treatment options are shown in Supplementary Table 1. Within each question, participants were asked to rate at least one response with a score of 9 if they use any of the designated treatment options. They were also asked to choose a score of 1 for all responses within a question if they do not take any of the actions described. The certified psychiatrists of the JSCNP were invited to participate in this survey by email. Those who agreed to participate completed the questionnaire. The survey took approximately 15 to 30 min to complete. The following participant information was also collected: age, sex, and work location.

2.2. Analysis

The following values were calculated for each treatment option: mean, standard deviation (SD), 95% confidence interval (CI), and number of responses of 1–3 (disagree), 4–6 (neutral), and 7–9 (agree). For each option, a Pearson's chi-squared test was performed to compare the frequencies in responses of 1–3, 4–6, and 7–9. When the responses were randomly distributed across these three types (i.e. disagree, neutral, and agree), as indicated by a p-value of ≥ 0.05 using a chi-squared test, it was considered that there was "no consensus" regarding the question. Treatment options with the lowest 95% CI of ≥ 6.5 were regarded as "first-line treatments;" those with the lowest 95% CI of ≥ 3.5 were considered "second-line treatments;" others were considered "third-line treatments." Options rated with 9 by more than 50% of the respondents were defined as "treatments of choice." In brief, the first-line treatment is usually appropriate as the initial treatment for a given situation (Allen et al., 2003). The treatment of choice, when it appears, is a particularly strong first-line recommendation. The second-line treatment is a reasonable option for patients who cannot tolerate or do not respond to the first-line treatment. The third-line treatment is usually inappropriate or used only when preferred alternatives were found to be ineffective.

3. Results

3.1. Characteristics of participants

Out of the 277 certified psychiatrists, 114 completed the questionnaire (response rate: 41.2%). Nineteen respondents (16.7%) were in their 30 s, 37 (32.5%) were in their 40 s, 36 (31.6%) were in their 50 s, 21 (18.4%) were in their 60 s, and 1 (0.9%) was 70 or older. The proportion of males was 92.1%. Forty-eight respondents (42.1%) were affiliated with university hospitals, 33 (28.9%) with general hospitals, 11 (9.6%) with psychiatric hospitals, 8 (7.0%) with community clinics, and 14 (12.3%) with other institutions such as government offices.

3.2. First-choice pharmacotherapy

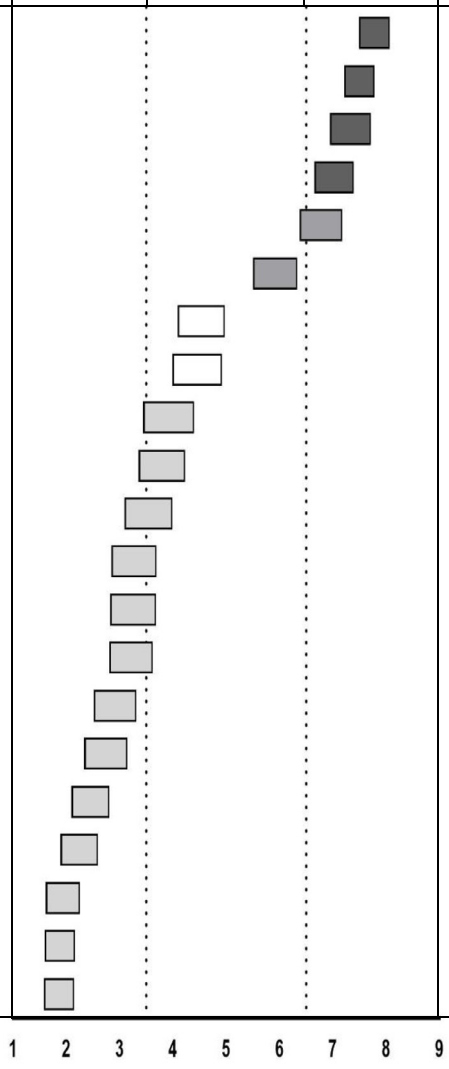
The following medications were categorized as first-line treatments for first-episode moderate-to-severe depression: mirtazapine (mean ± SD score, 7.8 ± 1.5, rated with 9 by 45.6% of the respondents), duloxetine (7.5 ± 1.5, rated with 9 by 32.5%), escitalopram (7.3 ± 2.1, rated with 9 by 43.0%), and venlafaxine (7.0 ± 2.0, rated with 9 by 28.9%) (Table 1). While other newer antidepressants followed these medications on agreement level, all tricyclic antidepressants (TCAs) and tetracyclic antidepressants (TeCAs) were grouped as third-line treatments.

The choice of first-line antidepressants varied depending on predominant symptoms (Table 2). Escitalopram (7.8 ± 1.7, treatment of choice, rated with 9 by 53.5% of the respondents) and sertraline (7.3 ± 1.7, rated with 9 by 28.4%) were likely to be selected for anxiety; duloxetine (7.6 ± 1.9, rated with 9 by 47.4%) and venlafaxine (7.2 ± 2.1, rated with 9 by 36.8%) were likely to be selected for loss of interest; and mirtazapine was likely to be selected for insomnia (8.2 ± 1.6, treatment of choice, rated with 9 by 64.0%), loss of appetite (7.9 ± 1.9, treatment of choice, rated with 9 by 57.9%), agitation and severe irritation (7.4 ± 2.0, rated with 9 by 43.0%), and suicidal ideation (7.5 ± 1.9, rated with 9 by 48.2%). Overall, TCAs, TeCAs, sulpiride, and trazodone were categorized as third-line treatments; however, trazodone was categorized as a second-line treatment for agitation and severe irritation (4.0 ± 2.4) and insomnia (5.9 ± 2.4), TeCAs were categorized as a second-line treatment for insomnia (4.2 ± 2.5), and sulpiride was categorized as a second-line treatment for loss of appetite (5.6 ± 2.7). There was no consensus regarding TCAs for agitation and severe irritation (4.4 ± 2.7) or suicidal ideation (4.4 ± 2.7).

First-line treatments for elderly patients with depression included mirtazapine (7.2 ± 1.8, rated with 9 by 30.7% of the respondents), sertraline (7.1 ± 1.8, rated with 9 by 30.7%), and escitalopram

Table 1
Consensus on Choice of Antidepressants for Moderate to Severe Depression.

	95% CI			Mean (SD)	Number of response 1	Number of response 1-3	Number of response 4-6	Number of response 7-9	Number of response 9
	Third-line	Second-line	First-line						
Mirtazapine				7.8 (1.5)	1	3	12	99	52
Duloxetine				7.5 (1.5)	1	2	23	89	37
Escitalopram				7.3 (2.1)	4	8	22	84	49
Venlafaxine				7.0 (2.0)	3	10	24	80	33
Sertraline				6.8 (2.2)	6	11	33	70	29
Paroxetine				5.9 (2.2)	9	18	36	60	10
Fluvoxamine				4.5 (2.4)	16	46	38	30	4
Milnacipran				4.5 (2.5)	23	43	42	29	5
Amoxapine				3.9 (2.6)	31	57	30	27	4
Trazodone				3.8 (2.3)	26	58	36	20	2
Clomipramine				3.5 (2.4)	35	65	29	20	2
Mianserin				3.3 (2.3)	39	69	35	10	3
Amitriptyline				3.3 (2.3)	39	67	31	16	3
Sulpiride				3.2 (2.2)	44	62	41	11	1
Imipramine				2.9 (2.2)	44	76	27	11	2
Nortriptyline				2.7 (2.2)	52	82	21	11	1
Maprotiline				2.5 (1.9)	57	88	20	6	1
Setiptiline				2.2 (1.9)	65	92	16	6	1
Dosulepin				1.9 (1.7)	73	99	11	4	1
Trimipramine				1.9 (1.5)	72	99	13	2	0
Lofepramine				1.9 (1.5)	72	100	11	3	0



Abbreviations: CI = confidence interval, SD = standard deviation.

Table 2
Consensus on Choice of Antidepressants depending on Predominant Symptoms.

	Anxiety	Loss of interest	Insomnia	Loss of appetite	Agitation and severe irritation	Suicidal ideation
Escitalopram	Best	2nd	2nd	2nd	2nd	2nd
Sertraline	1st	2nd	2nd	2nd	2nd	2nd
Fluvoxamine	no consensus	2nd	2nd	2nd	2nd	2nd
Paroxetine	2nd	2nd	no consensus	no consensus	no consensus	no consensus
Duloxetine	2nd	1st	no consensus	2nd	2nd	2nd
Venlafaxine	2nd	1st	no consensus	2nd	2nd	2nd
Milnacipran	2nd	no consensus	3rd	2nd	3rd	2nd
Mirtazapine	2nd	2nd	Best	Best	1st	1st
Trazodone	3rd	3rd	2nd	3rd	2nd	n.a.
Sulpiride	3rd	3rd	3rd	2nd	3rd	3rd
TCA	3rd	3rd	3rd	3rd	no consensus	no consensus
TeCA	3rd	3rd	2nd	3rd	3rd	3rd

Abbreviations: n.a. = not available, TCA = tricyclic antidepressant, TeCA = tetracyclic antidepressant.

(7.1 ± 2.0, rated with 9 by 36.0%) (Supplementary Table 1). On the other hand, all SNRIs were either categorized as second-line treatments (duloxetine: 6.6 ± 2.1 and venlafaxine: 6.4 ± 2.2) or there was no consensus (milnacipran; 4.5 ± 2.5). Sulpiride, TeCAs, and TCAs were considered third-line treatments.

Only SSRIs were categorized as first-line treatments for mild depression (7.6 ± 1.9, rated with 9 by 50.0% of the respondents) (Supplementary Table 1). Other newer antidepressants were categorized as second-line treatments, and other psychotropic medications, including herbal medicines, benzodiazepine anxiolytics, mood stabilizers, and atypical antipsychotics, were categorized as third-line treatments. The order of agreement levels for depressive symptoms in neurosis was similar to that for mild depression, but there was no first-line treatment (Supplementary Table 1). In contrast, all psychotropics were categorized as "no consensus" or as third-line treatments for depressive symptoms in borderline personality disorder except atypical antipsychotics, which were categorized as second-line treatments (6.1 ± 2.6) (Supplementary Table 1).

3.3. Pharmacological strategy for little or no response

Consensus on pharmacological strategy for partial response and non-response to newer antidepressants is shown in Table 3. The first-line treatment was switched to either an SNRI (7.7 ± 1.9, rated with 9 by 47.4% of the respondents) or mirtazapine (7.4 ± 2.0, rated with 9 by 39.5%) for non-response to an SSRI. On the other hand, the first-line treatment was switched to mirtazapine (7.1 ± 2.2, rated with 9 by 36.8%) for non-response to SNRI and to an SNRI (7.0 ± 2.3, rated with 9 by 36.8%) for non-response to mirtazapine; switching to an SSRI was categorized as a second-line treatment for both situations. Augmentation with an atypical antipsychotic or lithium, combination with another antidepressant, and switching to a TCA were categorized as second-line treatments for all non-response cases except for the following: there was no consensus on augmentation with olanzapine or quetiapine in the case of non-response to mirtazapine, augmentation with risperidone was considered a third-line treatment in all non-response cases, combination with an SSRI was considered a third-line treatment in the case of non-response to an SNRI, and there was no consensus on switching to a TCA in the case of non-response to an SNRI.

Regarding partial response to newer antidepressants, only augmentation with aripiprazole was categorized as a first-line treatment for partial response to an SSRI (7.1 ± 2.3, rated with 9 by 38.6% of the respondents) or SNRI (7.0 ± 2.5, rated with 9 by 39.5%). It was also ranked as a top second-line treatment for partial response to mirtazapine (6.8 ± 2.5). Switching to an SNRI or mirtazapine, augmentation with an atypical antipsychotic or lithium, and combination with another antidepressant were generally regarded as second-line treatments for all partial-response cases. On the other hand, switching to an SSRI was categorized as "no consensus" for all partial-response cases. Moreover, combination with an SSRI was rated as a third-line treatment for partial response to an SNRI. Augmentation with quetiapine was categorized as "no consensus" for partial response to mirtazapine, augmentation with brexpiprazole was categorized as "no consensus" for partial response to an SSRI, and augmentation with risperidone was considered a third-line treatment for all partial-response instances.

3.4. Discontinuation of pharmacotherapy

Various factors were considered to be involved in the decision to discontinue the first-line antidepressant treatment: duration of clinical stabilization (7.9 ± 1.5, rated with 9 by 48.2% of the respondents), presence/degree of side-effects (7.8 ± 1.6, rated with 9 by 48.2%), remaining symptoms (7.8 ± 1.6, rated with 9 by 39.5%), number of past episodes (7.7 ± 1.8, rated with 9 by 46.5%), severity when symptoms have deteriorated (7.7 ± 1.6, rated with 9 by 38.6%), patient's understanding of relapse prevention (7.7 ± 1.6, rated with 9 by 40.4%), patient's understanding of early signs of relapse (7.5 ± 1.6, rated with 9 by 31.6%), current social adaptation (7.4 ± 1.6, rated with 9 by 30.7%), understanding of the illness (7.3 ± 1.7, rated with 9 by 29.8%), past treatment responses (7.3 ± 1.8, rated with 9 by 32.5%), wish to have children (7.3 ± 1.9, rated with 9 by 31.6%), and current situational stressors (7.3 ± 2.0, rated with 9 by 29.8%) (Supplementary Table 1).

Regarding the timing of dose reduction or discontinuation of psychotropic medications used for augmentation after remission is achieved, the first-line option was "when a side-effect occurs" for the first episode (7.7 ± 1.8, rated with 9 by 46.5% of the respondents) and multiple episodes (7.6 ± 1.9, rated with 9 by 43.0%) (Supplementary

Table 3
Consensus on Choice of Pharmacological Strategy for No or Little Response.

	Non-response			Partial response		
	SSRI	SNRI	Mirtazapine	SSRI	SNRI	Mirtazapine
Switching: SNRI	1st	2nd	1st	2nd	2nd	2nd
Combination: SNRI	2nd	n.a.	2nd	2nd	n.a.	2nd
Switching: Mirtazapine	1st	1st	n.a.	2nd	2nd	n.a.
Combination: Mirtazapine	2nd	2nd	n.a.	2nd	2nd	n.a.
Switching: SSRI	2nd	2nd	2nd	no consensus	no consensus	no consensus
Combination: SSRI	n.a.	3rd	2nd	n.a.	3rd	2nd
Augmentation: Aripiprazole	2nd	2nd	2nd	1st	1st	2nd
Augmentation: Brexpiprazole	2nd	2nd	2nd	no consensus	2nd	2nd
Augmentation: Olanzapine	2nd	2nd	no consensus	2nd	2nd	2nd
Augmentation: Quetiapine	2nd	2nd	no consensus	2nd	2nd	no consensus
Augmentation: Lithium	2nd	2nd	2nd	2nd	2nd	2nd
Augmentation: Lamotrigine	no consensus	no consensus	no consensus	no consensus	no consensus	no consensus
Switching: TCA	2nd	no consensus	2nd	3rd	3rd	3rd
Combination: TCA	3rd	3rd	3rd	3rd	3rd	3rd
Switching: TeCA	3rd	3rd	3rd	3rd	3rd	3rd
Combination: TeCA	3rd	3rd	3rd	3rd	3rd	3rd
Switching: Sulpiride	3rd	3rd	3rd	3rd	3rd	3rd
Combination: Sulpiride	3rd	3rd	3rd	3rd	3rd	3rd
Switching: Trazodone	3rd	n.a.	n.a.	n.a.	3rd	3rd
Combination: Trazodone	3rd	3rd	3rd	3rd	3rd	3rd
Augmentation: Risperidone	3rd	3rd	3rd	3rd	3rd	3rd
Augmentation: Benzodiazepine	3rd	3rd	3rd	3rd	3rd	3rd

Abbreviations: n.a. = not available, SNRI = serotonin and noradrenaline reuptake inhibitors, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TeCA = tetracyclic antidepressant.

Table 1). The next option was "when a patient wishes to decrease the dose or discontinue." Apart from these options, a longer duration after remission received a higher agreement level for both first-episode and multiple-episode cases. "Indefinite use" was considered a third-line treatment for first-episode cases (3.5 ± 2.5), but there was no consensus for multiple-episode cases (5.1 ± 2.8).

On the other hand, the only first-line agreement regarding the duration of concomitant use of benzodiazepine anxiolytics was "pro re nata" (PRN) (7.0 ± 2.4, rated with 9 by 43.9% of the respondents) (Supplementary Table 1). As opposed to the discontinuation of medications used for augmentation, a shorter duration of concomitant use received a higher agreement level, following PRN.

4. Discussion

In the present study, treatment options for real-world clinical situations involving the treatment of depression that had not been sufficiently addressed in conventional treatment guidelines were evaluated by experts in Japan. These practical expert opinions suggest that pharmacological strategies for depression need to be flexible in consideration of each patient's needs and situation.

Previous guidelines generally refer to drug classes but not to individual drug names (e.g. SSRIs, SNRIs, mirtazapine, or bupropion as first-line treatments for MDD (American Psychiatric Association, 2010; Kennedy et al., 2016; Malhi et al., 2015)). One of the unique features of this expert consensus guideline is that recommendations for the choices of specific medications are clearly mentioned. Another difference is that treatment recommendations are provided for individual symptoms that are frequently encountered in clinical practice. While several treatment guidelines recommend psychotropic treatment choices based on depressive subtypes (e.g. melancholic and atypical features) (American Psychiatric Association, 2010; Kennedy et al., 2016; Malhi et al., 2015), there were a limited number of treatment guidelines to suggest specific antidepressant drugs depending on symptom profiles (Cleare et al., 2015; Kennedy et al., 2016). Depressive subtypes may not always be differential; treatment recommendations based on specific symptoms would be useful in the real-world clinical setting.

The Canadian Network for Mood and Anxiety Treatments clinical guidelines refer to specific drug recommendations for some symptoms, including vortioxetine, bupropion, duloxetine, and SSRIs for cognitive dysfunction; agomelatine, mirtazapine, and trazodone for sleep disturbance; and bupropion and SSRIs for fatigue (Kennedy et al., 2016). Furthermore, individual differences in response to pharmacological treatment have been investigated, and some evidence suggests the usefulness of choosing specific drugs according to predominant symptoms in the treatment of depression. For example, Uher et al. found that, while observed mood and cognitive symptoms improved more with escitalopram than with nortriptyline, neurovegetative symptoms improved more with nortriptyline than with escitalopram (Uher et al., 2009). Chekroud et al. reported that high doses of duloxetine outperformed escitalopram for core emotional symptoms, fluoxetine for sleep symptoms, and escitalopram, paroxetine, fluoxetine, and low-dose duloxetine for atypical symptoms (Chekroud et al., 2017). Additionally, sedative antidepressants seem to be preferable for depression with anxiety or insomnia, and activating antidepressants seem to be preferable for depression with psychomotor retardation (Malhi and Mann, 2018). In the present study, the experts may have chosen specific antidepressant drugs in consideration of patients' predominant symptoms and medication receptor profiles. For example, mirtazapine was preferred for cases with predominant symptoms of insomnia, loss of appetite, agitation and severe irritation, and suicidal ideation, probably because its H_1 receptor blockade presumably leads to sedation, somnolence, and weight gain; its 5-HT_{2c} receptor blockade leads to increased appetite, weight gain, and improved sleep; and its 5-HT_{2a} blockade leads to improved sleep (Millan, 2006). SNRIs were the only first-line antidepressants preferred in cases with loss of interest as the predominant symptom; although it is still speculative, these drugs are expected to act on drive through the noradrenergic system (Healy and McMonagle, 1997). SSRIs were the only first-line treatments preferred for cases with anxiety as the predominant symptom, possibly because only SSRIs are approved for anxiety disorders in Japan.

The choice of antidepressants varied depending on the severity of illness. Newer antidepressants were highly endorsed for moderate-to-severe depression, which is in line with several treatment guidelines (American Psychiatric Association, 2010; Bauer et al., 2013; Kennedy et al., 2016). Even though mirtazapine was categorized as a second-line treatment in one treatment guideline (Cleare et al., 2015), it was valued the most, possibly because of its high efficacy as reported in a recent network meta-analysis (Cipriani et al., 2018). For mild depression, SSRIs were chosen as the first-line treatment, SNRIs were chosen as the second-line treatment, and no consensus was reached on mirtazapine; this indicates that the experts think medications with high tolerability are favourable for mild depression. Given that current treatment guidelines generally recommend refraining from pharmacological treatments as the first-line treatment or using antidepressants only along with psychotherapy for mild depression (American Psychiatric Association, 2010; Kennedy et al., 2016; National Collaborating Centre for Mental Health (UK), 2010; World Health Organization, 2009), the potential risks and benefits of antidepressants should be taken into consideration before its use.

Mirtazapine was categorized as a first-line treatment for depression amongst elderly people. In contrast to this strong support, there has been only one report that examined the efficacy of mirtazapine in elderly patients with depression in a double-blind randomized controlled trial (Halikas, 1995). Moreover, whereas mirtazapine showed greater improvement in depressive symptoms than a placebo, it was more likely than placebo to be associated with side effects such as somnolence and dry mouth. This limited evidence and the possibly of more frequent adverse events should be considered when making a treatment decision. Sertraline and escitalopram were also considered first-line treatments, which is compatible with previous reviews and expert consensus guidelines that endorsed SSRIs as the first-line treatment for older patients (Alexopoulos et al., 2001; Kok and Reynolds, 2017; Taylor, 2014). In contrast, duloxetine and venlafaxine were recommended as second-line treatments. This may result from their potential risks of noradrenergic side effects such as urinary retention and elevated blood pressure (Carvalho et al., 2016). Moreover, duloxetine and venlafaxine had a higher risk for dizziness than placebo in a network meta-analysis that compared the efficacy and safety of SSRIs and SNRIs in elderly patients with depression (Thorlund et al., 2015). Additionally, while TCAs were considered for geriatric depression in some treatment guidelines (American Psychiatric Association, 2010; Bauer et al., 2015), they were categorized as third-line treatments in this study, possibly because of adverse events and drug interactions.

There were no first-line treatments for depressive symptoms in neurosis, which includes adjustment disorder, somatic symptom disorder, and borderline personality disorder. This may reflect physicians' struggle to use psychopharmacological treatments for these challenging populations. To our knowledge, there have been no psychotropic recommendations in the treatment guidelines for these disorders written in English, and just a few pharmacological recommendations have been included in the reviews for adjustment disorder and somatic symptom disorder (Kurlansik and Maffei, 2016; Stein, 2018). Regarding depressive symptoms in patients with borderline personality disorder, while the Cochrane review found that one study reported olanzapine to be superior when compared to fluoxetine (Stoffers et al., 2010), some treatment guidelines recommended SSRIs for affective dysregulation symptoms (American Psychiatric Association, 2001; Herpertz et al., 2007); yet another discouraged the use of pharmacological treatment (National Institute for Health and Care Excellence, 2009b). Evidence and experts' consensus suggest that pharmacological treatments should be considered carefully in these conditions.

Recommendations differed regarding regimen change, depending on previous medications and treatment response. In general, switching to another antidepressant was ranked high in the case of non-response to a previous antidepressant. While the first-line treatment for non-response to an SSRI was switching to an SNRI or mirtazapine, the treatment for non-response to an SNRI was switching to mirtazapine and vice versa. These sequential steps seem to imply the experts think SNRIs and mirtazapine are more effective than SSRIs. Augmentation with aripiprazole, olanzapine, or quetiapine was generally considered reasonable in the case of non-response based on clinical trial data (Zhou et al., 2015). However, there was no consensus regarding augmentation strategies with olanzapine and quetiapine for non-responders to mirtazapine, probably because the experts have concern about synergistic adverse effects such as increased appetite and weight gain due to the concomitant use of these medications. When it came to subsequent strategies for patients who partially responded to antidepressant treatment, augmentation therapy ranked relatively high. The experts may wish to maintain favourable effects with the ongoing treatment and further seek improvement with drugs that have different mechanisms of action. It is also noteworthy that, while augmentation with aripiprazole was categorized as a first-line treatment in the case of partial response to an SSRI or SNRI, it was considered a second-line treatment in the case of partial response to mirtazapine. This difference may be explained by the lack of evidence on the effectiveness of adjunctive aripiprazole added to mirtazapine.

No clear consensus was reached with regard to the timing of antidepressants or the discontinuation of adjunctive psychotropics in the treatment of depression. Multiple factors, including patients' present conditions, past histories, and insight of illness, were suggested to be considered when planning treatment discontinuation. Interestingly, indefinite use of adjunctive psychotropic drugs was categorized as "no consensus" for cases with multiple depressive episodes, despite the high risk of relapse (Berwian et al., 2017). On the other hand, due to potentially serious adverse events, it was recommended that benzodiazepines be prescribed as briefly as possible when concomitantly used for depression (Brandt and Leong, 2017).

There were several limitations to this study. First, this is an expert consensus guideline for the treatment of depression, which is considered to provide a low level of evidence. Many of the clinical questions included in this survey have not yet been fully addressed scientifically, which warrants further investigation of these controversial issues. Second, some questions may not have included sufficient information regarding the respondents' choices for treatment options. Heterogeneity of the patients should be acknowledged when the recommendations in this guideline are translated into clinical practice. Third, the generalizability of our findings may be limited, as all of the experts who participated in this study were Japanese. Moreover, some of the medications listed in the questionnaire are not available outside of Japan. Fourth, although we obtained responses from well over 100 specialists, the response rate of the questionnaire survey was relatively low. Fifth, objective assessment of exposure to psychotropic medications would ideally be taken into account in light of individual differences in pharmacokinetic parameters (Hiemke et al., 2018). Finally, our distinction of three categories (i.e. 1–3 (disagree), 4–6 (neutral), and 7–9 (agree)) and our methods of analysis were somewhat arbitrary.

In conclusion, Japanese experts choose pharmacological strategies for depression based on patients' clinical characteristics, treatment history, clinical settings, and drug receptor profiles. Although these recommendations need to be scientifically evaluated in future clinical trials, the clinical wisdom obtained from experts may be useful to guide management, especially in clinically challenging conditions for which the currently available evidence is limited.

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Supplementary materials

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