Review Article

CMJ

www.cmj.ac.kr

Optimizing the Use of Aripiprazole Augmentation in the Treatment of Major Depressive Disorder: From Clinical Trials to Clinical Practice

Changsu Han[1#], Sheng-Min Wang[2#], Soo-Jung Lee[3], Tae-Youn Jun[4] and Chi-Un Pae[3,5*]

[1]Department of Psychiatry, College of Medicine, Korea University, Seoul, [2]International Health Care Center, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, [3]Department of Psychiatry, Bucheon St. Mary's Hospital, The Catholic University of Korea College of Medicine, Busan, [4]Department of Psychiatry, St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea, [5]Department of Psychiatry and Behavioral Medicines, Duke University Medical Center, Durham, NC, USA

Major depressive disorder (MDD) is a recurrent, chronic, and devastating disorder leading to serious impairment in functional capacity as well as increasing public health care costs. In the previous decade, switching therapy and dose adjustment of ongoing antidepressants was the most frequently chosen subsequent treatment option for MDD. However, such recommendations were not based on firmly proven efficacy data from well-designed, placebo-controlled, randomized clinical trials (RCTs) but on practical grounds and clinical reasoning. Aripiprazole augmentation has been dramatically increasing in clinical practice owing to its unique action mechanisms as well as proven efficacy and safety from adequately powered and well-controlled RCTs. Despite the increased use of aripiprazole in depression, limited clinical information and knowledge interfere with proper and efficient use of aripiprazole augmentation for MDD. The objective of the present review was to enhance clinicians' current understanding of aripiprazole augmentation and how to optimize the use of this therapy in the treatment of MDD.

Key Words: *Antidepressive agents; Depressive disorder, Major; Aripiprazole*

[#] Both authors contributed equally as the first author to this work.

Article History:
received 16 July, 2015
revised 20 July, 2015
accepted 21 July, 2015

Corresponding Author:
Chi-Un Pae
Department of Psychiatry, Bucheon St. Mary's Hospital, The Catholic University of Korea College of Medicine, 2, Sosa-dong, Wonmi-gu, Bucheon 420-717, Korea
TEL: +82-32-340-7067
FAX: +82-32-340-2255
E-mail: pae@catholic.ac.kr

INTRODUCTION: WHY DO WE NEED ANOTHER TREATMENT OPTION FOR MAJOR DEPRESSIVE DISORDER?

Major depressive disorder (MDD) has a chronic and recurrent clinical course.[1] The prevalence of MDD is also common; one in six adults in the United States had at least one major depressive episode in the past year as of 2012.[1] The prevalence of MDD differs among countries; the estimated lifetime prevalence of major depressive episodes was 1.5% in Taiwan, 7% in Korea, 19.0% in Lebanon, 9.2% in Germany, and 9.0% in Chile.[2] Such differences may result from different concepts and thresholds in the diagnosis of MDD or limitations of epidemiological survey methods. MDD also produces huge public health care costs as the result of increased health care utilization and hospitalization associated with serious impairment in productivity, a higher suicide rate, more family conflicts, and reduced quality of life.[1]

Diverse antidepressants with different action mechanisms, such as selective serotonin reuptake inhibitors (SSRIs), dopamine-norepinephrine reuptake inhibitors (DNRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and noradrenergic and specific serotonin antagonists (NaSSAs), are available as a monotherapy for initial biological treatment of MDD. These antidepressants have been developed mainly under the monoamine hypothesis.[3-5] Recently, newer antidepressants such as vilazodone, vortioxetine, desvenlafaxine, and agomelatine have also been introduced on the market.[6-14] Despite the fact that the mainstay of treatment for MDD remains the use of antidepressants, the limited efficacy of contemporary anti-

http://dx.doi.org/10.4068/cmj.2015.51.2.66

depressants is well known. Thereby, the response and remission rates after antidepressant monotherapy are approximately 50-70% and 30%, respectively, in routine practice.[15,16] These rates have been consistently reported in numerous sponsor-initiated and independent randomized clinical trials (RCTs) as well as in a few large practical clinical trials such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D)[17] and Combining Medications to Enhance Depression Outcomes (CO-MED)[18] studies. In particular, the STAR*D trial showed that most MDD patients need additional treatment steps as the result of lower response and remission and higher relapse rates after initial treatment.[17] In addition, large meta-analyses have also proven the limited efficacy of antidepressants.[19-21] According to a recent subanalysis of the STAR*D trial,[22] significant functional impairment was clearly observed even in partial responders to citalopram at Level 1 exit, which was substantially different from the results in remitted patients in terms of quality of life, mental and physical functioning, and social and work-related impairment. That study clearly proposed the importance of controlling patients with partial response to achieve full remission and restoration of functioning.

WHICH STRATEGIES ARE POPULAR AS A SUBSEQUENT TREATMENT OPTION FOR MDD WHEN A PATIENT FAILS TO SHOW MEANINGFUL IMPROVEMENT AFTER ANTIDEPRESSANT MONOTHERAPY?

Most currently available treatment guidelines recommend that clinicians select a subsequent treatment option when patients do not respond or show only a partial response to initial antidepressant treatment (i.e., switch, combination, or augmentation therapy).[23-26] Each treatment option has different pros and cons according to the patients' clinical status, and there is no clear evidence supporting the superiority of one treatment modality over another.[27] Anecdotal data support the usefulness of switching or combining antidepressant strategies; however, few clinical trials of such therapies have been conducted and the results are inconsistent.[18,28-32] A number of small RCTs have investigated the efficacy of switching therapy for depression (10 RCTs and 30 open-label studies).[27,33-35] According to these controlled clinical trials, the remission rates after switching therapy ranged from 10% to 80%. In addition, switching to either a different class or within the same class of antidepressants is an intriguing clinical issue, but the number of high-quality studies that have investigated this issue remains limited. The results are also inconsistent, and thereby no clear evidence supports the superiority of either switching within a class or switching to a different class.

A handful of studies have tried to investigate the usefulness of antidepressant combination therapy.[36] Since the clinical trial of mianserin,[37,38] a few subsequent controlled trials were conducted mainly using the combination of mirtazapine with contemporary antidepressants.[36,39,40] For instance, according to the two studies by Blier et al.,[39,40] diverse combination therapy has better efficacy than monotherapy with a magnitude of difference of approximately 30% in the remission rate. However, the most recent large RCT of combination therapy conducted by Stewart et al.[41] completely failed to show any superiority of combination therapy over monotherapy in terms of timing of remission or the remission rate. These findings were also replicated in a recent large practical clinical trial, the CO-MED.[18] In the CO-MED, the remission and response rates as well as most secondary outcomes were not significantly different among treatment groups at the end of acute treatment. Such trends were also similar in the continuation phase, although remission and response rates were slightly increased in all treatment groups compared with the acute phase. In addition, combination therapy of mirtazapine and venlafaxine had a higher frequency of adverse events than did escitalopram monotherapy.

Non-antidepressant agents are also a popular subsequent treatment option for difficult-to-treat MDD patients. The available augmentation agents include mood stabilizers, T3, buspirone, and psychostimulants, but their utility is not supported by well-designed large RCTs. In addition, these agents have been used to augment only old formulations of antidepressants and not contemporary antidepressants.[42] Table 1 summarizes the data regarding currently available augmentation agents. Recently, augmentation of antidepressants with atypical antipsychotics (AAs) has dramatically increased in clinical practice because AAs (particularly aripiprazole and quetiapine ex-

TABLE 1. Summary of data for augmentation agents in the treatment of major depressive disorder from double-blind, randomized, placebo-controlled clinical trials (RCTs)

Agent	Number of RCTs	Results
Lithium	10	OR for response: 3.3
T3	3	2 trials positive, 1 trial negative
Stimulants	2	All failed
Modafinil	4	2 trials positive, 2 trials negative
Buspirone	3	All failed
Pindolol	12	Only 2 trials showed superior efficacy to placebo
Folic acid	2	Positive
Omega-3	7	4 trials negative, 3 trials positive
SAMe	1	Positive
Creatine Monohydrate	1	Positive
Testosterone	1	Positive
Mecamylamine/ Celecoxib/ Pramipexole	2/4/2	Positive/All positive/All failed
Atypical antpsychotics	26	Most trials showed positive results

OR: odds ratio, SAMe: S-adenosyl methionine.

tended release [XR]) have been officially approved by regulatory agencies owing to their proven efficacy and safety data from adequately powered and well-controlled RCTs.[43-47] Table 2 presents dosages and side effects of the currently available AAs used in clinical trials for patients with nonpsychotic depression.

WHICH STRATEGY IS MORE BENEFICIAL FOR TREATING PATIENTS WITH MDD?

Limited studies have looked into the differential effects and preferences of the subsequent treatment option for MDD. As seen in surveys by clinicians and the preferred treatment strategy in the STAR*D trial, augmentation therapy is preferred for partial responders.[48-53] Indeed, augmentation therapy may sustain the initial response from the first antidepressant and show additional effects with the augmented agent, whereas a switching strategy poses the risk of losing the benefits of the previously effective treatment.[54] Combination of antidepressants is also common in clinical practice and has an advantage generally similar to that of augmentation therapy; however, RCTs are still very limited.

A recent European naturalistic study showed that augmentation was preferred by physicians over switching or antidepressant combination therapies. Furthermore, AA or lithium augmentation was more effective than combining or switching antidepressants. However, the small sample size (total n=98) is an important limitation of this study.[28] In line with the findings by Köhler et al.,[28] a recent Korean naturalistic study[55] also found that patients have chosen AA therapy more than antidepressant combination and switching therapies when experiencing nonresponse to initial antidepressant treatment. In addition, AA therapy was shown to have more clinical benefit than antidepressant combination and switching. Recently, the first 6-week randomized study[56] directly compared effectiveness and tolerability between AAs and switching therapy. An inadequate response to antidepressants was defined as a total score ≥ 14 on the Hamilton Depression Rating Scale-item 17 (HDRS-17), although adequate antidepressant dosage for at least 6 weeks was used for treating the current depressive episode. The primary endpoint was change in the total score of the Montgomery-Åsberg Depression Rating Scale (MADRS) from baseline to the end of treatment. The study showed that the mean change in the MADRS score from baseline was significantly higher with AAs, with a difference in magnitude of -8.7, which was clinically very significant and already evident by week 2. The number of responders and remitters was also significantly higher with the AA treatment (60% and 54%, respectively) compared with switching (32.6% and 19.6%, respectively). AAs also showed better clinical outcomes compared with switching therapy for most secondary outcome measures. The tolerability profiles were comparable between the two groups. Despite the study's methodological shortcomings, the results suggested that AAs might produce better clinical outcomes than switching therapy in the treatment of MDD patients with inadequate responses to antidepressants. Some evidence suggests that AA augmentation may be more efficient and beneficial for treating MDD than switching and antidepressant combination therapies; however, we will need more definite data based on well-controlled direct comparison studies.

WHICH AUGMENTATION AGENT IS BETTER THAN OTHERS?

Interestingly, a recent network meta-analysis investigated the differential effects of various augmentation

TABLE 2. Dose ranges and common adverse events (AEs) of atypical antipsychotics in clinical trials for patients with nonpsychotic depression

Drug	Duration (week)	RCTs (n)	Dose Range	AEs
Olanzapine[a]	8-12	4	5-20 mg/d with various combinations, mean dose: 8-14 mg/d	Weight gain: 4 kg for 8 weeks
Risperidone[a]	4-6	5	0.5-3.0 mg/d, mean dose: 1.2-1.6 mg/d, 1-1.5 mg/d with minimal risk to developing AEs	Hyperprolactinemia
Quetiapine[a]	8-52	6	50-300 mg/d in flexible and fixed dose trials, mean dose: 180 mg/d	Sedation and weight gain
Aripiprazole[a]	6-52	6	3-15 mg/d, mean dose: 3-12 mg/d	Akathisia
Ziprasidone[b]	6	2	40-160 mg/d, mean dose in RCT was 96 mg/d	Most common AE was somnolence and fatigue in RCT
Amisulpride[c]	8-24	7	50 mg/d in MDD and dysthymia	Sexual dysfunction and weight gain
Asenapine, iloperidone, sertindole, and lurasidone	NA	0	NA, lurasidone under investigation yet	NA
Brexpiprazole	6	2	Two positive phase III RCTs	Akathisia and weight gain

MDD: major depressive disorder, EPS: extrapyramidal symptoms, NA: not available, [a]double-blind, randomized, (placebo)-controlled studies (RCTs), [b]monotherapy and augmentation therapy, [c]open-label and randomized controlled studies for MDD and dysthymia. From references 46, 47, 116-122. Aripiprazole and quetiapine XR have been officially approved by the US Food and Drug Administration.

agents by analyzing 18 RCTs (total n=4,422).[57] In the study, quetiapine (odds ratio [OR]=1.92), aripiprazole (OR=1.85), thyroid hormone (OR=1.84), and lithium (OR=1.56) were significantly more effective than placebo. The meta-analysis also proved that the efficacy of aripiprazole and quetiapine was more robust than that for thyroid hormone and lithium in sensitivity analyses. Only quetiapine 250-350 mg/d showed superiority over placebo in terms of all-cause discontinuation (OR=1.89). As for quality of life (function), aripiprazole and risperidone were proved to have benefit over placebo; additionally, risperidone showed greater efficacy than quetiapine. This network meta-analysis suggests that AAs may be more beneficial than other augmentation agents for treating patients with MDD. One interesting insurance claim data study (2006 through 2010) showed a recent usage trend for aripiprazole and quetiapine augmentation therapies in clinical practice.[58] Those who took US Food and Drug Administration (FDA)-recommended doses proportionally increased among the aripiprazole-treated patients (86.3% in 2006 to 94.5% in 2010), whereas quetiapine prescription failed to show such a trend (21.3% in 2006 to 24.0% in 2010). The quetiapine doses were less than those recommended by the US FDA. The authors indicated that aripiprazole augmentation should be prescribed at therapeutic doses for treating MDD itself, whereas quetiapine augmentation might be more targeted for treating specific symptoms such as insomnia and anxiety owing to its side effects such as sedation and somnolence. In this context, the preferential use of aripiprazole compared to other AAs has been consistently reported in many different studies. According to a recent survey study,[59] the rates of AAs used for MDD in Taiwan were aripiprazole (78.2%), quetiapine (62%), olanzapine (34.6%), risperidone (30.2%), and sulpiride (27.4%) which is in line with previous studies.[28,60] However, no direct comparison studies have been conducted. Clinical considerations on the use of aripiprazole augmentation will be discussed in detail in the later section.

INTRODUCTION OF ARIPIPRAZOLE AUGMENTATION FOR MDD

A number of small open-label studies and well-designed RCTs have proved the antidepressant augmentation effects of AAs.[45-47] Indeed, prescription of AAs has rapidly increased over the past decade and they are considered one of the most useful augmentation agents. Aripiprazole augmentation was approved by the US FDA in 2007. Aripiprazole augmentation has also been approved in a majority of Asian countries including Japan, the country which originally developed aripiprazole for the treatment of schizophrenia.

THE MECHANISM OF ACTION OF ARIPIPRAZOLE AUGMENTATION FOR MDD

We do not yet understand the clear mechanisms of action

TABLE 3. A summary of double-blind, randomized, placebo-controlled clinical trials (RCTs) of aripiprazole augmentation

Study (year)	Duration	Patients (n)	Primary end point	Response and remission rates
Berman et al. (2007)[67]	6 weeks	ARP: 181, PBO: 172	Change in MADRS total score PBO: −5.8, ARP: −8.8	Response: 33.7 vs 23.8%[a] Remission: 26 vs 15.7%[a]
Marcus et al. (2008)[68]	6 weeks	ARP: 185, PBO: 184	Change in MADRS total score PBO: −5.7, ARP: −8.5	Response: 32.4 vs 17.4%[a] Remission: 25.4 vs 15.2%[a]
Berman et al. (2009)[69]	6 weeks	ARP: 174, PBO: 169	Change in MADRS total score PBO: −6.4, ARP: −10.1	Response: 46.6 vs 26.6%[a] Remission: 36.8 vs 18.9%[a]
Fava et al. (2012)[70,b]	60 days, two phases	ARP: 56, PBO: 169	Difference in response rate by MADRS Total score Pooled, weighted ARP-PBO difference: 5.6%	ARP: 7.4% in phase 1 and 13.1% in phase 2 PBO: 9.58% in phase 1 and 6.4% in phase 2 Pooled, weighted ARP-PBO difference: 2.3%
Mischoulon et al. (2012)[71,b]	60 days, two phases		Mean change in MADRS total score (mean) in ARP: −9.5	Response: ARP 2 mg: 18.5%; ARP 5 mg: 12.8% PBO: 17.4% in phase 1 and 7.9% in phase 2
Kamijima et al. (2013)[72]	6 weeks	Placebo (n=195), fixed dose aripiprazole (n=197) or flexible dose aripiprazole (n=194)	Change in MADRS total score PBO: −7.4, ARP fixed: −10.5, ARP flexible: −9.6	Response: 39.2% for flexible-dose[a], 42.1% for fixed-dose[a], 28.2% for PBO[a] Remission: 30.4% for flexible-dose[a], 32.5% for fixed-dose[a], 20.5% for PBO[a]

MADRS: Montgomery-Åsberg Depression Rating Scale, ARP: aripiprazole, PBO: placebo, [a]$p<0.05$, ARP vs PBO, otherwise not significant, [b]Identical RCT and analyzed differently on primary objective.

of AAs as antidepressants. However, we can speculate on some potential action mechanisms (Table 3 and Fig. 1). Effects on the regulation of monoamine receptors and transporters leading to changes in monoamine transmission are a possible underlying mechanism of action of AA augmentation for treating MDD. These receptors and transporters include 5HT1A, 5HT2A/2B, 5HT2C, 5HT6, 5HT7, α-2 receptor, dopamine receptor, and norepinephrine transporter. Additional putative mechanisms are based on modification of hormones, the immune system, the sleep cycle, and neurotrophic factors.[61]

Likewise, the mechanism of action of aripiprazole augmentation for treating MDD may depend on diverse neurotransmitter receptors.[46,62] Aripiprazole has a partial agonistic effect on 5-HT1A receptor, and it also imposes 5-HT2A receptor antagonist with a partial dopamine D2/D3 agonist effect. Activation of 5-HT1A receptors is considered to regulate serotonin and dopamine balance in the prefrontal cortex and other brain areas relevant to MDD. 5-HT1A receptor agonists were found to be effective in the preservation of neuronal cells from the hazardous effects of glutamate or ischemia. 5-HT1A receptor agonists are also effective in hippocampal cell survival, whereas such an effect is antagonized by WAY-100635.[63,64] Blockage of 5-HT2A receptors elevates the extracellular levels of norepinephrine and leads to an antidepressant effect. Unlike other AAs, aripiprazole is a partial dopamine D2/D3 agonist with 30% intrinsic dopaminergic activity.[48] In addition, aripiprazole has low to moderate affinity for dopamine D4, serotonin 5-HT2c and 5-HT7, alpha1-adrenergic, and histamine H1 receptors, which might also be involved in its antidepressant property.[65] There is also an intriguing imaging study that investigated the action mechanism of aripiprazole augmentation for treating MDD.[66] The effects of aripiprazole augmentation on the cerebral utilization of 6-[^{18}F]-fluoro-3,4-dihydroxy-L-phenylalanine (FDOPA) was tested by using positron emission tomography (PET). Fourteen depressed patients who had failed 8 weeks of antidepressant therapy with SSRIs underwent FDOPA PET scans before and after aripiprazole augmentation. Eleven responded to aripiprazole augmentation. Interestingly, increased FDOPA trapping occurred in the right medial caudate in 10 of the 11 patients (91%) who showed a response to aripiprazole augmentation, whereas nonresponders demonstrated decreased right medial caudate FDOPA trapping.[66] The study also showed that the two symptoms showing the greatest improvement in responders were dopaminergic neurotransmission-related depressive systems such as lassitude and inability to feel. These results may suggest that the effects of aripiprazole augmentation may occur via alteration in dopaminergic activity or that dopaminergic involvement may be a key component of the anti-depressant effects.[66]

SUMMARY OF RCT EVIDENCE FOR ARIPIPRAZOLE AUGMENTATION THERAPY OF MDD

The clinical efficacy and safety of aripiprazole augmentation for treating patients with MDD were clearly proven in three identically designed initial phase RCTs[67-69] and three subsequent RCTs.[70-72] Table 4 summarizes the RCTs of aripiprazole augmentation for MDD. The mean change from baseline for the MADRS total score was the primary endpoint. Decrease of the MADRS total score from baseline to endpoint of more than 50% was defined as response. A decrease of 50% or more of the MADRS score along with a total MADRS score of 10 of less at the endpoint was considered remission. The remission rates were also significantly higher with aripiprazole augmentation (25.4% to 36.8%)

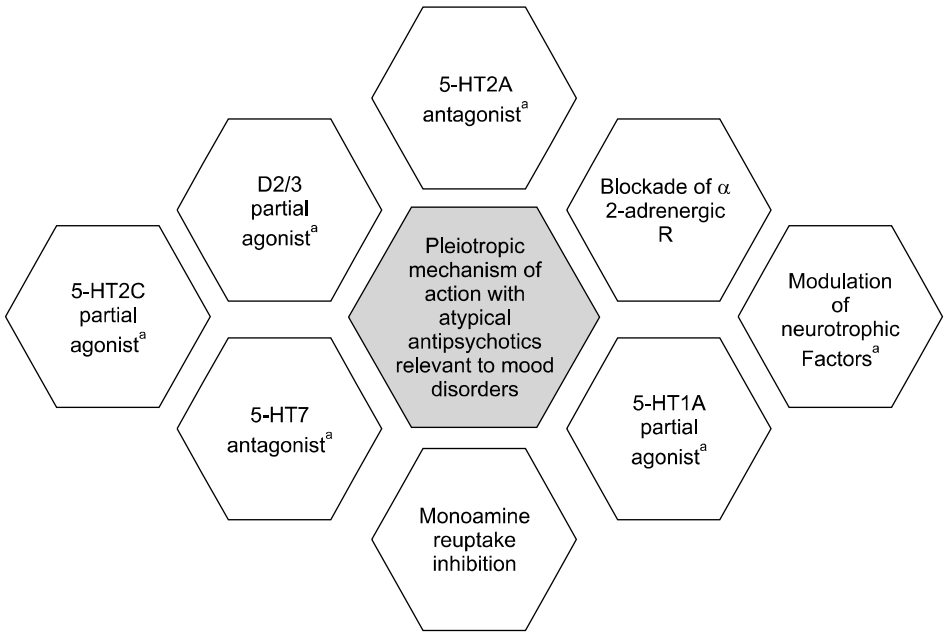

FIG. 1. Relevant action mechanisms of atypical antipsychotics as antidepressant augmentation therapy for major depressive. [a]Relevant for aripiprazole.

TABLE 4. Selected affinities of aripiprazole compared with antidepressants

Target K_i (nM)	Aripiprazole	Duloxetine	Imipramine	Desipramine	Mianserin
D_2	0.03	250	140	100	35
NET	1,200	24	58	0.12	150
SERT	1,400	0.02	0.36	42	>10,000
$5HT_{2A}$	0.74	>10,000	350	480	1.3
$5HT_{2C}$	33	3,000	330	630	1.4
$5HT_{1A}$	12	>10,000	760	730	2,300

NET: norepinephrine transporter, SERT: serotonin transporter, 5HT: serotonin, D: dopamine receptor.

than with placebo (15.2% to 18.9%).[67-69] In addition, significantly more patients taking aripiprazole augmentation achieved remission than patients taking placebo as early as week 1[67] and week 2.[68] A pooled analysis also confirmed the superior efficacy of aripiprazole augmentation over placebo.[73] Recently, the first 6-week Asian RCT (low fixed dose [3 mg/d] versus flexible dose [3-15 mg/d]; total n=392) was conducted in 2013 in Japan.[72] Patients who received either a low fixed dose or a flexible dose of aripiprazole experienced significantly greater improvement in their mean MADRS total score (−10.5 and −9.6, respectively) at study endpoint than did patients treated with adjunctive placebo (MADRS total score, −7.4). MADRS response rates at week 6 were significantly higher in the adjunctive aripiprazole groups (39.2% for flexible dose; 42.1% for low fixed-dose) than in the adjunctive placebo group (28.2%). Remission rates were also significantly higher in the adjunctive aripiprazole groups (30.4% for flexible dose; 32.5% for fixed dose) than in the adjunctive placebo group (20.5%). All those significant differences were evident as early as week 1. According to a recent meta-analysis, the blindness of the study did not influence the efficacy of aripiprazole augmentation for MDD, indicating the consistent efficacy of aripiprazole augmentation regardless of its use in both research and clinical settings.[74]

The safety of aripiprazole augmentation was consistently proved in well-designed RCTs.[67-69] When the three short-term studies were pooled, the completion rate of patients with aripiprazole augmentation (86%) was similar to that of placebo treatment (88%). In the pooled data, approximately 5% of patients with aripiprazole augmentation discontinued the study because of adverse events (AEs), whereas only 2% of patients receiving placebo treatment did. Mild to moderate akathisia was consistently the most frequent AE after aripiprazole augmentation (23%). In a pooled analysis,[75] the mean weight gain was significantly higher with aripiprazole augmentation than with placebo, with an estimated difference of 1.5 kg between two groups. The majority of laboratory studies clearly showed no meaningful differences between aripiprazole augmentation and placebo treatment in all short-term studies.[67-69] These favorable AE profiles were also replicated in the first Asian RCT by Kamijima and colleagues.[72] In the study, discontinuation due to AEs occurred in 2 patients (1.0%) in the placebo group, 5 patients (2.5%) in the aripiprazole fixed-dose group, and 5 patients (2.6%) in the aripiprazole flexible-dose group. Patients who experienced AEs leading to dose reduction were 6 (3.1%) in the placebo group, 17 (8.6%) in the aripiprazole fixed-dose group, and 33 (17.0%) in the aripiprazole flexible-dose group. The most common AEs in the aripiprazole groups were akathisia (37% vs 14%) and tremor (10% vs 7%), and the incidence was overall higher in the flexible-dose group than in the fixed-dose group. The majority of AEs were mild (aripiprazole flexible-dose 59.3%, fixed-dose 54.8%, placebo 48.7%) or moderate (17.0%, 15.7%, and 10.8%, respectively) in severity.

HOW TO OPTIMIZE THE USE OF ARIPIPRAZOLE AUGMENTATION IN CLINICAL PRACTICE

1. When is the proper time to augment with aripiprazole for patients with MDD?

On the basis of the inclusion criteria of the registry RCTs of aripiprazole augmentation and the fact that 70% of patients had a history of use of at least one antidepressant and that remission rates were significantly increased after two sequential antidepressant treatments,[17] aripiprazole augmentation can be tried for those who have a poor response to two initial antidepressant treatments. However, one Taiwanese study found that 2.5 mg/d of aripiprazole augmentation could be useful for treating drug-naïve MDD patients in combination with sertraline.[76] Those results suggested that aripiprazole augmentation could also be used in an earlier treatment stage for patients with MDD rather than wasting time until patients show an inadequate response to at least one antidepressant trial of adequate dose and duration. The fact that no differential efficacy of aripiprazole augmentation was shown regardless of past antidepressant treatment failure history (i.e., numbers and classes of prior antidepressants) in the subanalysis of the registry RCT data set is also noteworthy.[77]

2. How effective is aripiprazole augmentation in clinical practice?

The number needed to treat (NNT) and the number needed to harm (NNH) are easy and intuitive alternatives for clinicians to use in understanding complex clinical trial results.[78] In registry RCTs of aripiprazole augmentation, the NNTs for response and remission were 7 and 8, respec-

tively.[46] The results indicate that as many as 7 and 8 patients need to receive the aripiprazole augmentation for one additional patient to show response and remission. Concerning long-term effects, aripiprazole sustained its efficacy in a 52-week study. Indeed, almost 70% of patients scored 1 or 2 on the CGI-S at the end of treatment. This clearly showed the maintenance efficacy of aripiprazole augmentation and also contradicted the previous two double-blind discontinuation studies showing that patients who achieved symptom remission after risperidone augmentation did not maintain remission in a long-term follow-up.[79,80] However, data on more than 1 year of maintenance treatment are not yet available.

3. Is aripiprazole augmentation safe and tolerable regardless of duration of treatment for patients with MDD?

In a close look at the representative RCTs of AAs,[46] aripiprazole is found to have a strong relation with akathisia (NNH=6), whereas weight gain (NNH=3) and somnolence (NNH=5 for 300 mg/d and NNH=6 for 150 mg/d) were more significantly related to olanzapine and quetiapine XR, respectively, compared with placebo.[46,47,81] Careful consideration of the NNT and NNH for each AA can enable clinicians to practically weigh the benefit versus risk ratio and may help to select the best available AA in clinical practice. Serious AEs, such as tardive dyskinesia, did not occur in registry RCTs. According to a recent meta-analysis that included 18 clinical studies (n=5,531),[82] the overall proportion with metabolic syndrome (MetS) was 31% by use of any standardized MetS criteria. Compared with age- and gender-matched control groups, patients with MDD had a higher MetS prevalence (OR=1.5). They also had a higher risk for hyperglycemia (OR 1.3) and hypertriglyceridemia (OR 1.2). AA use was also significantly correlated with higher MetS prevalence estimates in MDD, whereas the prevalence of MetS was not moderated by age, gender, geographical area, smoking, antidepressant use, presence of psychiatric comorbidity, or timing of the data collection. The results clearly favored aripiprazole over other AAs including olanzapine and quetiapine as an augmentation therapy in terms of the risk of developing MetS.

Overall, the AE profile in the 52-week long-term trial was reported to be consistent with the results from the registry RCTs, and the most common AEs reported included akathisia (26%), fatigue (18%), and weight gain (17%).[83] Although there were four cases of probable tardive dyskinesia in the 52-week trial, the tardive dyskinesia spontaneously subsided after cessation of aripiprazole augmentation.

4. Are there differential effects of aripiprazole augmentation in accordance with disease characteristics such as subtype of MDD?

MDD patients with atypical or anxious features may have poorer clinical outcomes including higher baseline MDD severity and lower functional capacity than do those without such subsymptoms.[84,85] Subanalyses of previous clinical trials also showed different response and remission rates in accordance with the subtypes of MDD, such as anxious depression or atypical depression.[86,87] According to a pooled data set, aripiprazole was found to be an efficacious augmentation agent for patients with MDD regardless of subsymptoms, baseline severity of MDD, degree of prior treatment response, or a history of failure of initial antidepressant treatment.[88-92] Traditionally, MAOIs have been considered to be more favorable over tricyclic antidepressants (TCAs) for treating atypical MDD. However, there were no such differences in response and remission rates by antidepressant class in a subanalysis of aripiprazole augmentation RCTs.[93] The difference in mean reduction of the MADRS total score between the aripiprazole augmentation and placebo groups was -3 and -3.2, favoring aripiprazole augmentation over placebo for both between-class ($p<0.001$) and within-class ($p<0.001$) switching groups.[93] Relative risks for response were 1.6 for those who switched between classes and 1.7 for those who switched within a class.[93] According to a subanalysis by Stewart and colleagues,[94] aripiprazole augmentation produced greater improvement over placebo in the MADRS total score regardless of baseline MDD severity; the changes in the MADRS total score from baseline were -2.5 in mild, -3.2 in moderate, and -4.5 in severe groups, without statistical differences between subgroups. In additional, compared with placebo, aripiprazole augmentation increased the likelihood of response and remission in all subgroups of baseline severity of MDD. No robust clinical factors predicting response to augmentation antipsychotics have been found in patients with MDD. However, one subanalysis revealed that the presence of early response to aripiprazole augmentation as early as week 2 may strongly predict significantly more remission rates than in those who did not show a response.[95] Approximately 61% (44/72) of patients receiving aripiprazole augmentation who exhibited early response (week 2) achieved remission, whereas only 17% of non-early-responders showed remission at the study endpoint. The OR was almost 8 for prediction of early response to endpoint remission. Similarly, the recent Japanese RCT also showed that the superior efficacy of aripiprazole augmentation over placebo was not affected by numerous clinical factors (gender, age, number of previous antidepressant treatments, MDD diagnosis, number of past episodes, duration of illness, first onset age, type of antidepressants, or severity at the end of treatment).[72]

5. Can we use aripiprazole augmentation to treat patients who are not partial responders to their current antidepressant?

Most treatment guidelines suggest that augmentation therapy be used to treat partial responders to a current antidepressant, whereas switching therapy may be more suitable for treating those presenting with no or worsening response or tolerability issues with the current antidepressant. However, some subanalyses have clearly challenged such a traditional viewpoint, arguing that those recom-

mendations were not actually based on data from well-designed RCTs. In fact, they were proposed merely from clinical reasoning or on practical grounds. According to Nelson and colleagues' subanalysis of minimal responders to open-label antidepressant,[88] the time to response was significantly shorter for minimal responders taking aripiprazole augmentation (32 days) than for the placebo group (35.7 days). The minimal responders showed significantly higher response rates (36% vs. 19%) and higher remission rates (24% vs. 12%) with aripiprazole augmentation. Such differences were also evident as early as week 1 or 2. These trends were similar to those from subanalysis of partial responders to a current antidepressant. According to another subanalysis regarding worsening cases based on changes in the MADRS total score, the efficacy of aripiprazole augmentation was maintained regardless of such clinical factors.[96] According to the results, 15% of patients who completed the prospective treatment period were classified as having worsened MADRS, whereas 85% were considered not to have worsened MADRS. The difference in response rate between aripiprazole augmentation and placebo for patients who had worsened MADRS at the study endpoint was 14.1%, favoring aripiprazole augmentation over placebo. Similarly, the difference between aripiprazole augmentation and placebo was 15% at the study endpoint for patients whose symptoms did not worsen, also favoring aripiprazole augmentation over placebo. These trends were replicated in the remission rates (difference of 13% in patients whose symptoms worsened and 12.5% in those whose symptoms did not worsen). Therefore, the traditional preference in clinical practice for augmentation therapy only for partial responders and switching therapy for minimal or nonresponders should be revised, because aripiprazole augmentation may give a direct benefit and a more rapid response, which would improve clinical outcomes for both clinicians and patients. However, such findings must be replicated in prospectively well-designed and adequately powered RCTs before conclusions can be made.

6. What are the proper doses of aripiprazole for treating MDD?

Although the registry RCTs of aripiprazole augmentation did not specifically investigate the appropriate dosing strategy for aripiprazole augmentation, some generalizations can be made. The recommended dose of aripiprazole for MDD is 5-10 mg/d with a maximum dose of 15 mg/d according to the product label information. However, these recommendations were a consequence of design issues of the registry RCTs.[46] In those trials, the initiation dose was 5 mg/d and it was up-titrated weekly within 2-20 mg/d. The mean daily dose of aripiprazole was approximately 11-12 mg/day. The median dose was 10 mg/d and the modal dose was 5 mg/d. Overall, a terminal dose was evident at week 3 and it was maintained until the end of the study period. The class of antidepressants did not have any impact on the dosing trend.

Despite the lack of a strong dose-response relationship in most of the AA augmentation studies, increased intolerability has been found in accordance with dose increments of AAs.[46,47,97] Therefore, a low starting dose with slow titration to the target dose is prudent for achieving better efficacy and lesser AEs. A Japanese RCT[72] with a low-dose fixed (3 mg/d) and flexible-dose (3-15 mg/d) design also proved the significant effects of 3 mg/d of aripiprazole augmentation for treatment of MDD (mean dose=11 mg/d). The fact that a low mean dose of aripiprazole (3.8 mg/d) yielded substantial benefits over switching therapy is also noteworthy.[56] In the real-world setting the dose should be lower than what was originally believed to be necessary. Most experts now accept 1-3 mg as the initiation dose and 5-10 mg as the target dose. These new concepts for aripiprazole dosing are also supported by informative data from insurance claim studies[58] and retrospective studies[60] reflecting real-world clinical practice. Finally, we have to remember that aripiprazole augmentation shows a dose-response relationship in terms of the occurrence of akathisia. For instance, the akathisia rate was 37% in the dose range of 3-15 mg/d and 14% for the group receiving 3 mg/d,[72] and this dose-response relationship for akathisia was also consistently observed in previous RCTs.[67-69]

7. Are there differences in dosing patterns of aripiprazole augmentation between Asian and Western populations?

Given currently available data, 2-5 mg/d could be considered a low-dose aripiprazole augmentation, whereas 5-15 mg/d should be regarded a high dose. The low-dose data were mainly from Asian clinical trials, whereas the high-dose data were obtained from Western clinical trials. This difference may come from genetic differences in polymorphisms of cytochrome P450 2D6 (CYP2D6), which is the principal cause of pharmacokinetic variability in humans. Sufficient evidence suggests substantial racial differences in AA metabolism between Asians and Caucasians.[98,99] The CYP2D6*10 allele, which decreases CYP2D6 enzyme activity, is known to be highly prevalent in Asian populations but rare in Caucasians,[100] which may influence the pharmacokinetics of aripiprazole. This genetic difference may also lead to differential clinical outcomes and AEs by aripiprazole doses. Small-scale studies with Asians also proposed a potential difference in the proper doses of aripiprazole augmentation therapy.[16,101,102] The mean daily doses of augmentation aripiprazole ranged from 2 to 8 mg/d in Asians, whereas they were estimated to range from 11 to 12 mg/d in Caucasians. Subsequent research is mandatory to confirm whether such racial differences may exist in aripiprazole augmentation therapy for the treatment of MDD.

8. Is there a proper duration of treatment or appropriate time of discontinuation of aripiprazole augmentation?

No well-designed discontinuation study investigating this intriguing clinical issue is yet available. Currently, no consensus or prescription guide exists for aripiprazole augmentation. All of the short-term RCTs were designed

to observe aripiprazole efficacy only until 6 weeks after treatment, and open-label acute studies lasted no longer than 12 weeks.[103,104] Hence, clinicians may consider aripiprazole augmentation for at least 6 weeks and up to 12 weeks to see an acute response. However, when we consider the results from the 52-week maintenance trial, aripiprazole augmentation could be utilized for 1 year after achieving remission. Aripiprazole is basically an antipsychotic that can lead to unwanted AEs such as tardive dyskinesia. Indeed, tardive dyskinesia is one of the serious AEs that can be caused by any antipsychotic. Most treatment guidelines do not specifically address this clinical issue, but experts recommend that clinicians gradually taper aripiprazole augmentation within 3 to 6 months after achieving remission, although it is not mandatory. In our clinical practice, some patients who had already achieved remission experienced relapse or worsening of MDD symptoms immediately after early discontinuation of aripiprazole. The data regarding early termination of aripiprazole augmentation after achieving remission or response are still not sufficient. Therefore, adequately powered, controlled clinical trials should be conducted to address this issue in the near future.

9. What else can we expect from aripiprazole augmentation?

According to insurance data analysis of health care utilization and expenditures,[105] the mean costs for aripiprazole were significantly lower than those for olanzapine and quetiapine for most service types, including all-cause medical care, mental health, and mental-health-related medical care. In addition, aripiprazole had significant effects in reducing the duration and chance of hospitalization and the use of the emergency department compared with quetiapine in patients having MDD. Clinicians may consider currently available pharmaco-economic vigilance data in clinical practice. Aripiprazole was also efficacious and safe for chronic and recurrent MDD,[104] as well as for elderly populations.[106] In the subanalysis by Steffens et al,[106] elderly patients on aripiprazole showed significantly greater reduction (3.6 points more) in MADRS total score versus the placebo group at the endpoint, which was similar to the improvement observed in younger patients. Remission rates were also significantly higher with aripiprazole versus placebo in older (15.4% difference) and younger (10.5% difference) patients. Akathisia was the most common AE in both populations, but the incidence was higher in younger (26.0%) than in elderly (17.1%) patients. It is also notable that simultaneous aripiprazole augmentation with SNRI produced a huge response and remission rates in a previous study, indicating that clinicians may promptly use aripiprazole augmentation at the beginning of antidepressant treatment according to the patient's clinical status.[103] Well-controlled clinical trials or naturalistic studies of the role of aripiprazole augmentation for treating MDD patients with comorbid medical diseases are lacking, although some anecdotal data suggest that aripiprazole may be beneficial in the treatment of eating disorders, nicotine/alcohol dependence, behavioral disturbances due to neuropsychiatric diseases (brain injury, epilepsy, etc), and neurological motor disease.[15,77,107-111] MDD is commonly comorbid with medical diseases such as diabetes mellitus and cardiovascular diseases in routine clinical practice. These comorbid conditions are known to negatively impact the clinical course and prognosis of patients with MDD.[112] Hence, it will be intriguing and necessary for clinicians to investigate the potential role of aripiprazole in the treatment of MDD with comorbid medical diseases in the future.

10. What barriers to aripiprazole augmentation therapy exist?

The prescription pattern of clinicians in the selection of certain medications may be influenced by various factors, especially when the candidate medication is originally approved for different diseases and also when the candidate medication (antipsychotic) is in fact originally not for the specific disorder of interest (MDD). The level of evidence with medication, personal experience, knowledge about the medication, health insurance, and reimbursement and payment policies may also affect clinicians' choice of certain medications in clinical practice.[113-115] An interesting study used a survey to investigate the factors influencing the prescription of aripiprazole augmentation in Taiwan.[59] Even though the most frequently used antipsychotic was aripiprazole, the study showed that the main reason psychiatrists did not choose aripiprazole was because of its higher price leading to insurance audit. In contrast to the American Psychiatric Association's willingness to appeal the use of innovative treatments with insurance companies and regulatory agencies, these authors asserted that the Taiwanese Society of Psychiatry has taken little action against insurance audits.[59] In fact, the prescribing behavior of psychiatrists may influence the outcomes of refractory MDD and may cause a delay in the use of adequate antipsychotic augmentation therapy.[59] It is important, therefore, for health policy makers to understand the prescribing behaviors and modify the insurance policy accordingly if a newer agent is available on the market. Clinical factors other than the insurance issue that circumvent the use of aripiprazole augmentation may include clinicians being afraid to use antipsychotics for MDD patients. Theses prejudices could be reduced by continuing medical education (CME) or scientific symposiums by opinion leaders and clinical experts. Indeed, the pharmacodynamics profile of aripiprazole surpasses that of some of antidepressants.[46] In addition, the use of generic formulations can reduce medical costs if bioequivalence is fully achieved compared with the original formulation.

CONCLUSIONS

Evidence supporting the beneficial effects and tolerability of AAs for the treatment of MDD as an augmentation therapy has been dramatically increasing in recent days, particularly for those patients who showed a partial re-

Table 5. Clinical considerations in the use of aripiprazole augmentation for major depressive disorder (MDD)

-Aripiprazole augmentation has consistently shown its efficacy for MDD through adequately powered and well-controlled clinical trials
-The efficacy of atypical antipsychotics as augmentation therapy has been found to be similar across such agents; however, safety and tolerability of atypicals may substantially differ
-Metabolic syndrome is a raising clinical concern in treatment of patients with MDD; hence, the risk of metabolic side effects must be carefully weighed against clinical benefits when prescribing atypicals as augmenting agents. Evidence indicates that aripiprazole has a more favorable metabolic profile than others
-Dose titration should be done carefully so as to minimize side effects and optimize therapeutic benefits. Initiation doses of aripiprazole augmentation should be 1-3 mg/d and 5-10 mg/d for target doses.
-Wait and increase the dose less than 5 mg/d by two weeks (i.e., 2 mg/d by a week) under consideration of its pharmacokinetic profile when observing partial or no improvement with good tolerability.
-Dose increase could be stopped for observation of maximal benefits at the current dose when observing meaningful improvement with good tolerability. Too rapid up-titration may result in transient gain and possibly cause loss of efficacy.
-When stopped aripiprazole augmentation for a while, reinstatement should resume the first use of aripiprazole augmentation not the last dose.
-Ethnic difference is clearly proposed in terms of dosing of aripiprazole due to different genetic polymorphism of CYP2D6 10 allele between Asian and Western populations.
-The effects of aripiprazole augmentation may be equally retained regardless of the subtypes of depression (i.e., anxious or atypical depression).
-Tapering issue may need more well controlled clinical trials. Gradual tapering off within 3 to 6 months should be proper after achievingremission.
-Data suggest that aripiprazole augmentation can be maintained up to 52 weeks; however, benefit/risk of long-term use of aripiprazole may need to await more high-quality data.
-Aripiprazole augmentation is beneficial not only for partial responders to current antidepressant but also for minimal responders and those who worsen with current antidepressants.
-The effect of aripiprazole augmentation is not influenced by diverse clinical factors such as gender, age, number of adequate ant depressant trials in the current episode, number of depressive episodes, duration of the MDD episode, age at first onset, duration of illness, antidepressant class (SSRI vs SNRI), or baseline severity of MDD.
-Early response to aripiprazole augmentation by 2 weeks may strongly predict the better response and remission at the end of short-term treatment (ie 6 weeks).
-Augmentation, antidepressant switching and antidepressant combination therapies have differential pros/cons based on patients' own clinical status and there had been no clear evidence supporting a superiority of one treatment modality over the other till today. Only limited naturalistic data propose more benefit of augmentation therapy over other strategies.
-Direct comparison studies between aripiprazole and other augmentation agents for MDD need more clear data. Some limited data sugest superiority of aripiprazole augmentation over other treatment option (i.e., antidepressant switching therapy).

SSRI: selective serotonin reuptake inhibitor, SNRI: serotonin-norepinephrine reuptake inhibitor.

sponse to initial antidepressants despite adequate dosing and treatment duration. Aripiprazole was the first AA approved as an augmentation agent for the treatment of MDD. However, differential effects among the AAs used as augmentation agents for treating MDD have not been fully studied. Such studies may be difficult to conduct because of sponsorship issues. Therefore, naturalistic studies concerning this issue may be helpful for clinicians to address whether one specific AA may have more benefit over other AAs for treating MDD. In fact, some insurance claim data have suggested that aripiprazole may have been used for MDD itself, whereas quetiapine XR was used to control specific symptoms of MDD (ie, sleep and anxiety).

Which augmentation agent is more beneficial or harmful for specific groups of patients? Comparison among AAs, lithium, thyroid medications, and other augmentation agents have not been sufficiently conducted. However, studies have indicated that aripiprazole augmentation may be more beneficial compared with other augmentation agents (ie, lithium and T3) and other treatment options (ie, switch and combination). Hence, subsequent large RCTs or practical clinical trials should be conducted to address a clear benefit-to-risk ratio of aripiprazole augmentation for treating patients with MDD compared with other augmentation agents in routine clinical practice.

Informative clinical considerations based on various findings from RCTs for the prudent use of aripiprazole augmentation for treating MDD in clinical practice are listed in Table 5. These recommendations will be helpful for clinicians who may want to use aripiprazole for the first time for treating their MDD patients or for those who have some issues with the use of aripiprazole augmentation. Future studies of aripiprazole augmentation should have more specific and targeted designs to address the many clinical issues about real-world, optimal utilization of AA augmentation therapy in the treatment of MDD.

ACKNOWLEDGEMENTS

This study was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI12C0003).

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003; 289:3095-105.
2. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health 2013;34:119-38.
3. Fava M, Rush AJ, Trivedi MH, Nierenberg AA, Thase ME, Sackeim HA, et al. Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study. Psychiatr Clin North Am 2003;26:457-94.
4. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163:28-40.
5. Wang SM, Han C, Pae CU. Criticisms of drugs in early development for the treatment of depression: what can be improved? Expert Opin Investig Drugs 2015;24:445-53.
6. Wang SM, Han C, Lee SJ, Patkar AA, Masand PS, Pae CU. Vilazodone for the treatment of major depressive disorder: focusing on its clinical studies and mechanism of action. Psychiatry Investig 2015;12:155-63.
7. Han C, Pae CU. Pain and depression: a neurobiological perspective of their relationship. Psychiatry Investig 2015;12:1-8.
8. Pae CU. Desvenlafaxine in the treatment of major depressive disorder. Expert Opin Pharmacother 2011;12:2923-8.
9. Pae CU. Desvenlafaxine: a new antidepressant or just another one? Expert Opin Pharmacother 2009;10:875-87.
10. Pae CU. Agomelatine: a new option for treatment of depression? Expert Opin Pharmacother 2014;15:443-7.
11. Wang SM, Han C, Lee SJ, Patkar AA, Masand PS, Pae CU. A review of current evidence for vilazodone in major depressive disorder. Int J Psychiatry Clin Pract 2013;17:160-9.
12. Pae CU, Wang SM, Han C, Lee SJ, Patkar AA, Masand PS, et al. Vortioxetine: a meta-analysis of 12 short-term, randomized, placebo-controlled clinical trials for the treatment of major depressive disorder. J Psychiatry Neurosci 2015;40:174-86.
13. Pae CU, Park MH, Marks DM, Han C, Patkar AA, Masand PS. Desvenlafaxine, a serotonin-norepinephrine uptake inhibitor for major depressive disorder, neuropathic pain and the vasomotor symptoms associated with menopause. Curr Opin Investig Drugs 2009;10:75-90.
14. Pae CU, Wang SM, Han C, Lee SJ, Patkar AA, Masand PS, et al. Vortioxetine, a multimodal antidepressant for generalized anxiety disorder: a systematic review and meta-analysis. J Psychiatr Res 2015;64:88-98.
15. Pae CU. Evidence-based treatment for depressive disorder. Psychiatry Investig 2015;12:278-9.
16. Pae CU, Patkar AA, Jun TY, Lee C, Masand PS, Paik IH. Aripiprazole augmentation for treatment of patients with inadequate antidepressants response. Depress Anxiety 2007;24: 522-6.
17. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905-17.
18. Rush AJ, Trivedi MH, Stewart JW, Nierenberg AA, Fava M, Kurian BT, et al. Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. Am J Psychiatry 2011;168:689-701.
19. Papakostas GI, Thase ME, Fava M, Nelson JC, Shelton RC. Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. Biol Psychiatry 2007;62:1217-27.
20. Papakostas GI, Fava M. A meta-analysis of clinical trials comparing milnacipran, a serotonin--norepinephrine reuptake inhibitor, with a selective serotonin reuptake inhibitor for the treatment of major depressive disorder. Eur Neuropsychopharmacol 2007;17:32-6.
21. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet 2009;373:746-58.
22. Dennehy EB, Marangell LB, Martinez J, Balasubramani GK, Wisniewski SR. Clinical and functional outcomes of patients who experience partial response to citalopram: secondary analysis of STAR*D. J Psychiatr Pract 2014;20:178-87.
23. Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association. Am J Psychiatry 2000;157(4 Suppl):1-45.
24. Bauer M, Whybrow PC, Angst J, Versiani M, Möller HJ; World Federation of Societies Biological Psychiatry Task Force on Treatment Guidelines for Unipolar Depressive Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Acute and continuation treatment of major depressive disorder. World J Biol Psychiatry 2002;3:5-43.
25. Anderson IM, Ferrier IN, Baldwin RC, Cowen PJ, Howard L, Lewis G, 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.
26. Kennedy SH, Lam RW, Cohen NL, Ravindran AV; CANMAT Depression Work Group. Clinical guidelines for the treatment of depressive disorders. IV. Medications and other biological treatments. Can J Psychiatry 2001;46 Suppl 1:38S-58S.
27. Connolly KR, Thase ME. If at first you don't succeed: a review of the evidence for antidepressant augmentation, combination and switching strategies. Drugs 2011;71:43-64.
28. Köhler S, Unger T, Hoffmann S, Steinacher B, Fydrich T, Bschor T. Comparing augmentation with non-antidepressants over sticking to antidepressants after treatment failure in depression: a naturalistic study. Pharmacopsychiatry 2013;46:69-76.
29. 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.
30. Thase ME. Antidepressant combinations: widely used, but far from empirically validated. Can J Psychiatry 2011;56:317-23.
31. Pae CU, Han C, Jun TY. Do we need more than one antidepressant for patients with major depressive disorder? Expert Rev Neurother 2011;11:1561-4.
32. Pae CU, Wang SM, Lee SY, Lee SJ. Early switch strategy in patients with major depressive disorder. Expert Rev Neurother 2012;12:1185-8.
33. Poirier MF, Boyer P. Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. Br J Psychiatry 1999;175:12-6.
34. Lenox-Smith AJ, Jiang Q. Venlafaxine extended release versus citalopram in patients with depression unresponsive to a selective serotonin reuptake inhibitor. Int Clin Psychopharmacol 2008;23:113-9.
35. Souery D, Serretti A, Calati R, Oswald P, Massat I, Konstantinidis A, et al. Citalopram versus desipramine in treatment resistant depression: effect of continuation or switching strategies: a randomized open study. World J Biol Psychiatry 2011; 12:364-75.
36. Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biol Psychiatry 2002;51:183-8.
37. Ferreri M, Lavergne F, Berlin I, Payan C, Puech AJ. Benefits from mianserin augmentation of fluoxetine in patients with major depression non-responders to fluoxetine alone. Acta Psychiatr Scand 2001;103:66-72.
38. Licht RW, Qvitzau S. Treatment strategies in patients with major depression not responding to first-line sertraline treatment. A randomised study of extended duration of treatment, dose increase or mianserin augmentation. Psychopharmacology (Berl) 2002;161:143-51.
39. Blier P, Ward HE, Tremblay P, Laberge L, Hébert C, Bergeron R. Combination of antidepressant medications from treatment initiation for major depressive disorder: a double-blind randomized study. Am J Psychiatry 2010;167:281-8.
40. Blier P, Gobbi G, Turcotte JE, de Montigny C, Boucher N, Hébert C, et al. Mirtazapine and paroxetine in major depression: a comparison of monotherapy versus their combination from treatment initiation. Eur Neuropsychopharmacol 2009;19:457-65.
41. Stewart JW, McGrath PJ, Blondeau C, Deliyannides DA, Hellerstein D, Norris S, et al. Combination antidepressant therapy for major depressive disorder: speed and probability of remission. J Psychiatr Res 2014;52:7-14.
42. Philip NS, Carpenter LL, Tyrka AR, Price LH. Augmentation of antidepressants with atypical antipsychotics: a review of the current literature. J Psychiatr Pract 2008;14:34-44.
43. Pae CU, Patkar AA. Clinical issues in use of atypical antipsychotics for depressed patients. CNS Drugs 2013;27 Suppl 1: S39-45.
44. Han C, Yeh TL, Kato M, Sato S, Chang CM, Pae CU. Management of chronic depressive patients with residual symptoms. CNS Drugs 2013;27 Suppl 1:S53-7.
45. Han C, Wang SM, Kato M, Lee SJ, Patkar AA, Masand PS, et al. Second-generation antipsychotics in the treatment of major depressive disorder: current evidence. Expert Rev Neurother 2013;13:851-70.
46. Pae CU, Forbes A, Patkar AA. Aripiprazole as adjunctive therapy for patients with major depressive disorder: overview and implications of clinical trial data. CNS Drugs 2011;25:109-27.
47. Pae CU, Sohi MS, Seo HJ, Serretti A, Patkar AA, Steffens DC, et al. Quetiapine XR: current status for the treatment of major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2010;34:1165-73.
48. Mischoulon D, Nierenberg AA, Kizilbash L, Rosenbaum JF, Fava M. Strategies for managing depression refractory to selective serotonin reuptake inhibitor treatment: a survey of clinicians. Can J Psychiatry 2000;45:476-81.
49. Gaynes BN, Dusetzina SB, Ellis AR, Hansen RA, Farley JF, Miller WC, et al. Treating depression after initial treatment failure: directly comparing switch and augmenting strategies in STAR*D. J Clin Psychopharmacol 2012;32:114-9.
50. Rush AJ, Warden D, Wisniewski SR, Fava M, Trivedi MH, Gaynes BN, et al. STAR*D: revising conventional wisdom. CNS Drugs 2009;23:627-47.
51. Wisniewski SR, Fava M, Trivedi MH, Thase ME, Warden D, Niederehe G, et al. Acceptability of second-step treatments to depressed outpatients: a STAR*D report. Am J Psychiatry 2007; 164:753-60.
52. Warden D, Rush AJ, Wisniewski SR, Lesser IM, Kornstein SG, Balasubramani GK, et al. What predicts attrition in second step medication treatments for depression?: a STAR*D report. Int J Neuropsychopharmacol 2009;12:459-73.
53. Papakostas GI, Petersen TJ, Green C, Iosifescu DV, Yeung AS, Nierenberg AA, et al. A description of next-step switching versus augmentation practices for outpatients with treatment-resistant major depressive disorder enrolled in an academic specialty clinic. Ann Clin Psychiatry 2005;17:161-5.
54. Shelton RC. What are the comparative benefits and harms of augmentation treatments in major depression? J Clin Psychiatry 2015;76:e531-3.
55. Han C, Wang SM, Seo HJ, Lee BC, Jeon HJ, Kim W, et al. Aripiprazole augmentation, antidepressant combination or switching therapy in patients with major depressive disorder who are partial- or non-responsive to current antidepressants: a multi-center, naturalistic study. J Psychiatr Res 2014;49:75-82.
56. Han C, Wang SM, Kwak KP, Won WY, Lee H, Chang CM, et al. Aripiprazole augmentation versus antidepressant switching for patients with major depressive disorder: A 6-week, randomized, rater-blinded,prospective study. J Psychiatr Res 2015;66-67:84-94.
57. Zhou X, Ravindran AV, Qin B, Del Giovane C, Li Q, Bauer M, et al. Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. J Clin Psychiatry 2015;76:e487-98.
58. Jing Y, Guo Z, Kalsekar I, Forbes RA, Hebden T, Thase ME. Dosing patterns of aripiprazole and quetiapine for adjunctive treatment of major depressive disorder (2006-2010). Int Clin Psychopharmacol 2013;28:87-90.
59. Hsu YC, Chou YC, Chang HA, Kao YC, Huang SY, Tzeng NS. Dilemma of prescribing aripiprazole under the Taiwan health insurance program: a descriptive study. Neuropsychiatr Dis Treat 2015;11:225-32.

60. Pae CU, Wang SM, Han C, Lee SJ, Patkar AA, Masand PS. Aripiprazole augmentation for major depressive disorder: dosing patterns in a naturalistic treatment setting. Int Clin Psychopharmacol 2014;29:116-9.
61. Sagud M, Mihaljević-Peleš A, Begić D, Vuksan-Ćusa B, Kramarić M, Zivković M, et al. Antipsychotics as antidepressants: what is the mechanism? Psychiatr Danub 2011;23:302-7.
62. Chen TY, Tzeng NS. Aripiprazole: a dopamine modulator that mimics methylphenidate in producing faster antidepressant effects. Med Hypotheses 2013;81:183-5.
63. Fricker AD, Rios C, Devi LA, Gomes I. Serotonin receptor activation leads to neurite outgrowth and neuronal survival. Brain Res Mol Brain Res 2005;138:228-35.
64. Radley JJ, Jacobs BL. 5-HT1A receptor antagonist administration decreases cell proliferation in the dentate gyrus. Brain Res 2002;955:264-7.
65. Otsuka Pharmaceuticals I. Prescribing information: Aripiprazole 2009.
66. Conway CR, Chibnall JT, Cumming P, Mintun MA, Gebara MA, Perantie DC, et al. Antidepressant response to aripiprazole augmentation associated with enhanced FDOPA utilization in striatum: a preliminary PET study. Psychiatry Res 2014;221:231-9.
67. Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2007;68:843-53.
68. Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol 2008;28:156-65.
69. Berman RM, Fava M, Thase ME, Trivedi MH, Swanink R, McQuade RD, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. CNS Spectr 2009;14:197-206.
70. Fava M, Mischoulon D, Iosifescu D, Witte J, Pencina M, Flynn M, et al. A double-blind, placebo-controlled study of aripiprazole adjunctive to antidepressant therapy among depressed outpatients with inadequate response to prior antidepressant therapy (ADAPT-A Study). Psychother Psychosom 2012;81:87-97.
71. Mischoulon D, Witte J, Levy M, Papakostas GI, Pet LR, Hsieh WH, et al. Efficacy of dose increase among nonresponders to low-dose aripiprazole augmentation in patients with inadequate response to antidepressant treatment: a randomized, double-blind, placebo-controlled, efficacy trial. J Clin Psychiatry 2012;73:353-7.
72. Kamijima K, Higuchi T, Ishigooka J, Ohmori T, Ozaki N, Kanba S, et al; ADMIRE Study Group. Aripiprazole augmentation to antidepressant therapy in Japanese patients with major depressive disorder: a randomized, double-blind, placebo-controlled study (ADMIRE study). J Affect Disord 2013;151:899-905.
73. Thase ME, Trivedi MH, Nelson JC, Fava M, Swanink R, Tran QV, et al. Examining the efficacy of adjunctive aripiprazole in major depressive disorder: a pooled analysis of 2 studies. Prim Care Companion J Clin Psychiatry 2008;10:440-7.
74. Pae CU, Seo HJ, Lee BC, Seok JH, Jeon HJ, Paik JW, et al. A meta-analysis comparing open-label versus placebo-controlled clinical trials for aripiprazole augmentation in the treatment of major depressive disorder: lessons and promises. Psychiatry Investig 2014;11:371-9.
75. Fava M, Wisniewski SR, Thase ME, Baker RA, Tran QV, Pikalov A, et al. Metabolic assessment of aripiprazole as adjunctive therapy in major depressive disorder: a pooled analysis of 2 studies. J Clin Psychopharmacol 2009;29:362-7.
76. Lin CH, Lin SH, Jang FL. Adjunctive low-dose aripiprazole with standard-dose sertraline in treating fresh major depressive disorder: a randomized, double-blind, controlled study. J Clin Psychopharmacol 2011;31:563-8.
77. Pae CU, Serretti A, Patkar AA, Masand PS. Aripiprazole in the treatment of depressive and anxiety disorders: a review of current evidence. CNS Drugs 2008;22:367-88.
78. Citrome L. Number needed to treat: what it is and what it isn't, and why every clinician should know how to calculate it. J Clin Psychiatry 2011;72:412-3.
79. Rapaport MH, Gharabawi GM, Canuso CM, Mahmoud RA, Keller MB, Bossie CA, et al. Effects of risperidone augmentation in patients with treatment-resistant depression: Results of open-label treatment followed by double-blind continuation. Neuropsychopharmacology 2006;31:2505-13.
80. Alexopoulos GS, Canuso CM, Gharabawi GM, Bossie CA, Greenspan A, Turkoz I, et al. Placebo-controlled study of relapse prevention with risperidone augmentation in older patients with resistant depression. Am J Geriatr Psychiatry 2008;16: 21-30.
81. Citrome L. Adjunctive aripiprazole, olanzapine, or quetiapine for major depressive disorder: an analysis of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Postgrad Med 2010;122:39-48.
82. Vancampfort D, Correll CU, Wampers M, Sienaert P, Mitchell AJ, De Herdt A, et al. Metabolic syndrome and metabolic abnormalities in patients with major depressive disorder: a meta-analysis of prevalences and moderating variables. Psychol Med 2014;44:2017-28.
83. Berman RM, Thase ME, Trivedi MH, Hazel JA, Marler SV, McQuade RD, et al. Long-term safety and tolerability of open-label aripiprazole augmentation of antidepressant therapy in major depressive disorder. Neuropsychiatr Dis Treat 2011;7:303-12.
84. Stewart JW, McGrath PJ, Fava M, Wisniewski SR, Zisook S, Cook I, et al. Do atypical features affect outcome in depressed outpatients treated with citalopram? Int J Neuropsychopharmacol 2010;13:15-30.
85. Fava M, Rush AJ, Alpert JE, Balasubramani GK, Wisniewski SR, Carmin CN, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am J Psychiatry 2008;165:342-51.
86. Stewart JW. Treating depression with atypical features. J Clin Psychiatry 2007;68 Suppl 3:25-9.
87. Liebowitz MR, Quitkin FM, Stewart JW, McGrath PJ, Harrison WM, Markowitz JS, et al. Antidepressant specificity in atypical depression. Arch Gen Psychiatry 1988;45:129-37.
88. Nelson JC, Thase ME, Bellocchio EE, Rollin LM, Eudicone JM, McQuade RD, et al. Efficacy of adjunctive aripiprazole in pa-

tients with major depressive disorder who showed minimal response to initial antidepressant therapy. Int Clin Psychopharmacol 2012;27:125-33.
89. Nelson JC, Mankoski R, Baker RA, Carlson BX, Eudicone JM, Pikalov A, et al. Effects of aripiprazole adjunctive to standard antidepressant treatment on the core symptoms of depression: a post-hoc, pooled analysis of two large, placebo-controlled studies. J Affect Disord 2010;120:133-40.
90. Trivedi MH, Thase ME, Fava M, Nelson CJ, Yang H, Qi Y, et al. Adjunctive aripiprazole in major depressive disorder: analysis of efficacy and safety in patients with anxious and atypical features. J Clin Psychiatry 2008;69:1928-36.
91. Thase ME, Demyttenaere K, Earley WR, Gustafsson U, Udd M, Eriksson H. Extended release quetiapine fumarate in major depressive disorder: analysis in patients with anxious depression. Depress Anxiety 2012;29:574-86.
92. Bauer M, El-Khalili N, Datto C, Szamosi J, Eriksson H. A pooled analysis of two randomised, placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. J Affect Disord 2010;127:19-30.
93. Dunner DL, Laubmeier KK, Manos G, Forbes RA, Baker RA, Berman RM. Beneficial effects of adjunctive aripiprazole in major depressive disorder are not dependent on antidepressant therapy history: a post hoc analysis of 3 randomized, double-blind, placebo-controlled trials. Prim Care Companion CNS Disord 2012;14. doi: 10.4088/PCC.12m01380. [Epub ahead of print]
94. Stewart TD, Hatch A, Largay K, Sheehan JJ, Marler SV, Berman RM, et al. Effect of symptom severity on efficacy and safety of aripiprazole adjunctive to antidepressant monotherapy in major depressive disorder: a pooled analysis. J Affect Disord 2014;162:20-5.
95. Casey DE, Laubmeier KK, Marler SV, Forbes RA, Baker RA. Efficacy of adjunctive aripiprazole in major depressive disorder: a pooled response quartile analysis and the predictive value of week 2 early response. Prim Care Companion CNS Disord 2012;14. doi: 10.4088/PCC.11m01251. [Epub ahead of print]
96. Nelson JC, Rahman Z, Laubmeier KK, Eudicone JM, McQuade RD, Berman RM, et al. Efficacy of adjunctive aripiprazole in patients with major depressive disorder whose symptoms worsened with antidepressant monotherapy. CNS Spectr 2014;19: 528-34.
97. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. Am J Psychiatry 2009;166:980-91.
98. Shen H, He MM, Liu H, Wrighton SA, Wang L, Guo B, et al. Comparative metabolic capabilities and inhibitory profiles of CYP2D6.1, CYP2D6.10, and CYP2D6.17. Drug Metab Dispos 2007;35:1292-300.
99. Chong SA, Tan CH, Khoo YM, Lee HS, Wong KE, Ngui F, et al. Clinical evaluation and plasma clozapine concentrations in Chinese patients with schizophrenia. Ther Drug Monit 1997; 19:219-23.
100. Ji L, Pan S, Marti-Jaun J, Hänseler E, Rentsch K, Hersberger M. Single-step assays to analyze CYP2D6 gene polymorphisms in Asians: allele frequencies and a novel *14B allele in mainland Chinese. Clin Chem 2002;48:983-8.
101. Chen SJ, Hsiao YL, Shen TW, Chen ST. The effectiveness and safety of adjunctive aripiprazole in Taiwanese patients with antidepressant-refractory major depressive disorder: a prospective, open-label trial. J Clin Psychopharmacol 2012;32:56-60.
102. Yoshimura R, Kishi T, Hori H, Ikenouchi-Sugita A, Katsuki A, Umene-Nakano W, et al. Comparison of the efficacy between paroxetine and sertraline augmented with aripiprazole in patients with refractory major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatr 2012;39:355-7.
103. Nierenberg AA, Trivedi MH, Gaynes BN, Mitchell J, Davis LL, Husain MM, et al. Effectiveness study of Venlafaxine-XR combined with aripiprazole for chronic or recurrent major depressive disorder. Aust N Z J Psychiatry 2009;43:956-67.
104. Pae CU, Jeon HJ, Lee BC, Seo HJ, Kim SG, Park EJ, et al. Aripiprazole augmentation for treatment of patients with chronic or recurrent major depressive disorder: a 12-week prospective open-label multicentre study. Int Clin Psychopharmacol 2013;28:322-9.
105. Jing Y, Kalsekar I, Curkendall SM, Carls GS, Bagalman E, Forbes RA, et al. Intent-to-treat analysis of health care expenditures of patients treated with atypical antipsychotics as adjunctive therapy in depression. Clin Ther 2011;33:1246-57.
106. Steffens DC, Nelson JC, Eudicone JM, Andersson C, Yang H, Tran QV, et al. Efficacy and safety of adjunctive aripiprazole in major depressive disorder in older patients: a pooled subpopulation analysis. Int J Geriatr Psychiatry 2011;26:564-72.
107. Jang H, Kim SH, Park SH, Choo IH, Kim SG. Psychiatric symptoms in temporal lobe epilepsy with left mesial hippocampal sclerosis. Psychiatry Investig 2015;12:274-7.
108. Geoffroy PA, Goddefroy G, Rolland B, Cottencin O. Efficacy of aripiprazole in comorbid addiction in bipolar disorder. CNS Neurosci Ther 2012;18:359-60.
109. Jayaram N, Rao NP, Venkatasubramanian G, Behere RV, Varambally S, Gangadhar BN. Successful use of aripiprazole for delusional disorder with comorbid pituitary microadenoma: a case report. Psychosomatics 2011;52:395-7.
110. Starrenburg FC, Bogers JP. How can antipsychotics cause Diabetes Mellitus? Insights based on receptor-binding profiles, humoral factors and transporter proteins. Eur Psychiatry 2009; 24:164-70.
111. Koh JS, Ko HJ, Wang SM, Cho KJ, Kim JC, Lee SJ, et al. The relationship between depression, anxiety, somatization, personality and symptoms of lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Psychiatry Investig 2015; 12:268-73.
112. Park SC, Lee HY, Sakong JK, Jun TY, Lee MS, Kim JM, et al. Distinctive clinical correlates of psychotic major depression: the CRESCEND study. Psychiatry Investig 2014;11:281-9.
113. Zetin M, Hoepner CT, Bjornson L. Rational antidepressant selection: applying evidence-based medicine to complex real-world patients. Psychopharmacol Bull 2006;39:38-104.
114. Liu YM, Ou HT, Yang YK. Choice of generic versus brand-name antidepressants in a regulated prescription drug market: evidence from Taiwan. J Ment Health Policy Econ 2014;17:163-72.
115. Donohue JM, Zhang Y, Aiju M, Perera S, Lave JR, Hanlon JT, et al. Impact of Medicare Part D on antidepressant treatment,

medication choice, and adherence among older adults with depression. Am J Geriatr Psychiatry 2011;19:989-97.
116. Owenby RK, Brown LT, Brown JN. Use of risperidone as augmentation treatment for major depressive disorder. Ann Pharmacother 2011;45:95-100.
117. Dunner DL, Amsterdam JD, Shelton RC, Loebel A, Romano SJ. Efficacy and tolerability of adjunctive ziprasidone in treatment-resistant depression: a randomized, open-label, pilot study. J Clin Psychiatry 2007;68:1071-7.
118. Rocca P, Marchiaro L, Rasetti R, Rivoira E, Bogetto F. A comparison of paroxetine versus paroxetine plus amisulpride in the treatment of dysthymic disorder: efficacy and psychosocial outcomes. Psychiatry Res 2002;112:145-52.
119. Rocca P, Fonzo V, Ravizza L, Rocca G, Scotta M, Zanalda E, et al. A comparison of paroxetine and amisulpride in the treatment of dysthymic disorder. J Affect Disord 2002;70:313-7.
120. Zanardi R, Smeraldi E. A double-blind, randomised, controlled clinical trial of acetyl-L-carnitine vs. amisulpride in the treatment of dysthymia. Eur Neuropsychopharmacol 2006;16:281-7.
121. Liebowitz M, Lam RW, Lepola U, Datto C, Sweitzer D, Eriksson H. Efficacy and tolerability of extended release quetiapine fumarate monotherapy as maintenance treatment of major depressive disorder: a randomized, placebo-controlled trial. Depress Anxiety 2010;27:964-76.
122. Papakostas GI, Fava M, Baer L, Swee MB, Jaeger A, Bobo WV, et al. Ziprasidone augmentation of escitalopram for major depressive disorder: efficacy results from a randomized, double-blind, placebo-controlled study. Am J Psychiatry 2015:appiajp 201514101251. [Epub ahead of print]