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Review

Antidepressant therapy

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Abstract

This review is intended to promote the awareness of depression and to familiarize readers with antidepressant therapy. The theme is to let the readers know that depression is popular and incapacitating, but easily treatable. The topics of the review include the diagnosis of depression, a brief history of antidepressant development, the monoamine hypothesis of depression, functional classification of antidepressants, defining remission as the goal in antidepressant therapy, tips in maximalizing and potentiating antidepressant therapy. Then, the drugs of antidepressants are glamorized to include the improvement in pain symptoms, stress urinary incontinence, and various health benefits including improved immunity. The drug lag problems in Japan in 1990's and 2010 are also highlighted. The author finally summarizes current status of available antidepressant drugs on the Japanese market with an optimistic prediction that the prescription of antidepressants will steadily become popular.

Key words: diagnosis for depression, antidepressant drugs, dosage of antidepressant, duration of antidepressant use, remission from depression

Introduction

Abraham Lincoln (1809–1865), the 16th US president; Ernest Hemingway (1899–1961), a writer; as well as Marilyn Monroe (1926–1962), an actress and model were three well-known famous Americans who suffered from depression. Soseki Natsume (1867–1916), a writer at Meiji Era; Kanoko Okamoto (1889–1939), a writer and poet; Akira Kurosawa (1910–1990), a film director; Jiro Tamiya (1935–1978), an actor; Akiko Koyama (1935–), a film actress; Nana Kinomi (1946–), an actress and singer; as well as Anna Ogino (1956–), a writer and novelist were or are among Japanese celebrities who had or have depression.

Depression is the most common mental disorder nowadays. In the United States of America, the 12-month prevalence of major depressive disorder is about 7% (American Psychiatric Association [APA], 2013). The prevalence in 18- to 29-year-old individuals is threefold higher than that in those age 60 years or older (APA, 2013). Females have 1.5- to 3-fold higher rates than males beginning in early adolescence (APA, 2013). Nine percent of men and 18% of women have depression once in their lifetime, and more than 10% of the population have more than two episodes of depression (Hasin et al., 2005).

The World Health Organization predicts that depression is going to be the number one disease in the burden of mental disorders (Lee, 2016). Depression can lower the quality of life remarkably and influence one's life in various aspects, namely impairing the ability to eat, sleep, work, and interact with other persons (Lee, 2016). A person with depression loses interest, motivation, and self-esteem. But some persons with depression have suicidal idea, and even commit suicide. Psychiatrists have put much energy in finding the cause and developing drug to treat depression (Lee, 2016).

Most people with depression do not seek treatment although the great majority even those whose depression is extremely severe can be helped. Thanks to years of wonderful research, many medications are available to ease the pain of depression. Unfortunately, many people do not recognize that depression is a treatable illness.

In this review, the author does not plan to do a comprehensive encyclopedic review on antidepressant therapy. I neither plan to list all pivotal clinical drug trials leading to regulatory approval of any antidepressant. I just intend to give a bird's-eye view on the topic "antidepressant therapy" to target at the readership of non-medical professional staff such as nurses, physiotherapists, occupational therapists, or other healthcare clinicians in Japan. Hopefully, the information presented here may help the readers to refer those sufferers to get proper treatment.

The Diagnosis of Depression

Depression is an episodic disease. A "major depressive episode" is called if the patient has accumulated depressive symptoms and signs mounting to a clinically significant severity. Major depressive episode can be primarily from major depressive disorder, bipolar disorder ; or secondary from physical conditions or substance use disorders (APA, 2013).

To the patients themselves, the most incapacitating aspect, in depression is the obvious adjustment problems to cope with the pressure from the job, and to impair occupational functions, resulting in letting the patients feel miserable, and/or having poor job performance, or poor interpersonal relationship (APA, 2013).

Commonly seen cluster of symptoms and signs due to a major depressive episode consists of (A) low mood, (B) lack of interest, (C) 5% or more of body weight changes, (D) sleeping disturbances, (E) irritability or being withdrawn, (F) fatigue, (G) guilt, (H) poor concentration, and (I) suicidal risk (suicidal idea, suicidal attempts, preoccupation on death theme and over-purchase of life insurance).

For a diagnosis of avoiding false positive cases, the diagnosis for a major depressive disorder needs a least one symptom of (A) or (B), and 5 of the 9 symptoms listed above (APA, 2013). The listing of the above nine symptoms is according to the occurrence frequencies of major depressive disorder patients. In the context of this review, the author just uses "depression" to mean a major depressive episode from major depressive disorder unless specifically defined.

A Brief History of Antidepressant Development

The introduction of chlorpromazine in 1952 was a great historical advancement and commercial success in psychopharmacology (López-Muñoz 2005 ; Shen 1999). In an attempt and a process of finding a substituted antipsychotic drug chlorpromazine (Figure 1), Kuhn in Switzerland serendipitously discovered the first tricyclic antidepressant (TCA) imipramine (G-22,355) in 1957

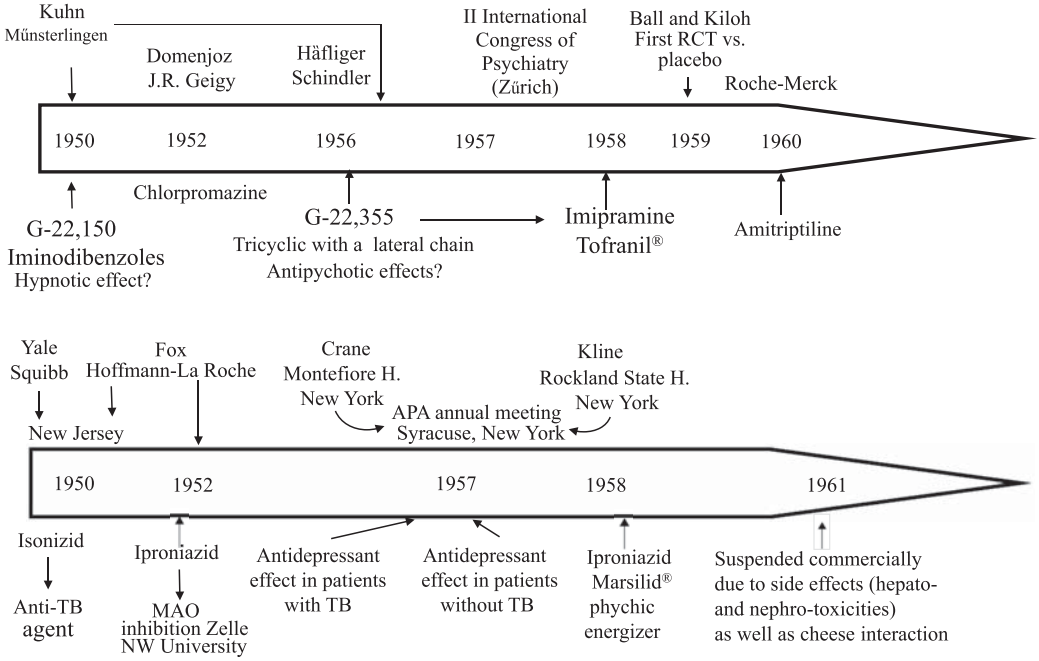

Figure 1 Schematic demonstrations for key events in discovering imipramine and iproniazid. RCT, randomized controlled trial ; APA, American Psychiatric Association ; TB, tuberculosis : MAO, monoamine oxide. Reproduced from López-Muñoz et al., 2014 with permission from Taiwanese Society of Psychiatry.

(López-Muñoz et al., 2014). In the same year, a monoamine oxidase inhibitor (MAOI) iproniazid was also serendipitously found to provide antidepressant effect in tuberculotic and non-tuberculotic patients by Crane and Kline in USA, respectively (López-Muñoz et al., 2014).

When fluoxetine, the first selective serotonin reuptake inhibitor (SSRI) (Wong et al. 1995), was approved by US Food and Drug Administration in 1987, the antidepressant development was moved from the era of TCAs into SSRIs, which have been noted to have less side effects than those associated with TCA's and MAOIs. Finally, serotonin and norepinephrine reuptake inhibitors (SNRIs, including venlafaxine, minacipran, and duloxetine) were introduced to improve remission rates.

In 2017, partial serotonin reuptake agonists (such as vilazodone, vortioxetine, etc.) have been the main focus of antidepressant developments in an attempt to relieve the side effects of SSRIs and SNRIs (Shen 2011a). The state of arts of antidepressant treatment for the clinicians, in my opinion, is to know how to teach the clinicians and patients to use the existing antidepressants instead of inventing brand new antidepressants (Figure 2).

Monoamine Hypothesis of Depression

When clinicians started to treat depression in late 1950s with imipramine, a TCA or with iproniazid, an MAOI, they did not know the cause of depression clearly except genetic factor, knowing that the patients who have family members diagnosed with depression, have higher possibility to have depression (Freis et al., 1954).

In the early 1950s, many psychiatrists started to know that depression is not just because of congenital or innate tendency and environmental stress. But they considered depression as neurophysiological abnormality of the brain. The reason why this theory is developed is that many patients who have hypertension and tuberculosis have shown prominent depressive symptoms (Lee, 2016). Several cases from many medical institutions have been reported that patients who have hypertension and take anti-hypertensive drugs over long periods of time generate severe depression (Freis et al., 1954), or that patients with tuberculosis treated with isoniazid show improved depressive symptoms (López-Muñoz et al., 2014 ; Oquendo et al., 2001).

At this time, the causative agent of depression is monoamine abnormalities of the brain because several studies have proven that the fact that anti-hypertensive drugs decrease monoamine in brain (Shore et al., 1955), and anti-tuberculotic drugs inhibit breakdown of monoamine (López-Muñoz et al., 2014). The hypothesis that depression occurs due to decreased monoamine transmission in the brain was well-established after Glowinski and Axelrod (1964) used an isotope-tracing method, demonstrating that imipramine and related compounds block the reuptake of epinephrine in the brain. In a double-blind placebo-controlled cross-over tryptophan depletion study demonstrating the importance of brain serotonin, 6 of 20 subjects with a family history of depression and none of 19 subjects without a family history of depression showed a depressive mood when screened for depression (Benkelfat et al. 1994).

Norepinephrine (noradrenalin), dopamine and serotonin are three different types of monoamines. These three monoamines play a critical

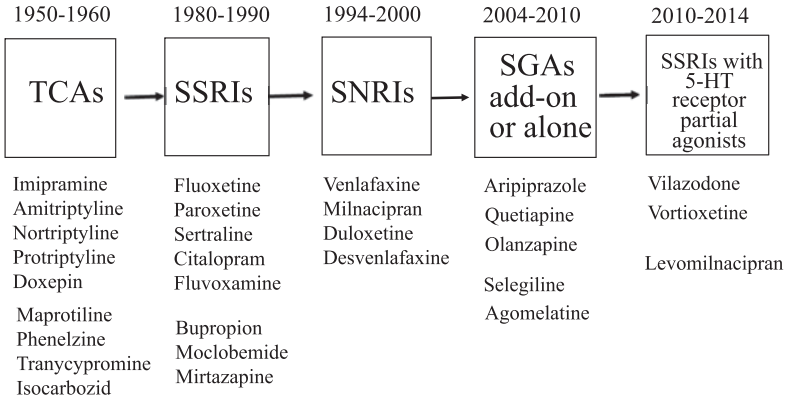

Figure 2 A history of antidepressant drugs. TCAs, tricylic antidepressants ; SSRIs, selective serotonin reuptake inhibitors ; SNRIs, serotonin and norepinephtine reuptake inhibitors ; SGAs, second-generation antipsychotics ; 5-HT, serotonin. Expanded from Shen, 2011b with permission to reprint from Taiwanese Society of Psychiatry.

rôle in developing depression by experimenting on animals (Carlsson et al., 1957 ; Hatotani et al., 1984). In the animal studies, the investigators found that serotonin and norepinephrine are major monoamines to develop depression although dopamine has been found to be implicated in some clinical cases (Shen 2011a). These three monoamines determine the neurotransmission between the narrow gaps of synapses for neuronal connections in the brain. Depression develops when the amount of serotonin released is scarce, or when the amount of norepinephrine or dopamine is too much (Shen 2011a). These amounts of neurotransmitters are different and are genetically determined.

In an oversimplified pharmacologic concept, an antidepressant works on improving the neurotransmission between the gaps of pres- and postsynaptic neurons (Shen 2011a). Antidepressant therapy can cause a series of signal transduction cascades to produce either more coupled stimulating G-protein (through the increased serotonin action), or more coupled inhibitory G-protein (through less norepinephrine action), consequently to increase protein kinase A and calcium-depending kinase, respectively. Those two increased kinases in the cytoplasma can increase concentration of c-AMP regulatory element binding (CREB) inside the neuclei, resulting in increased brain-derived neurotrophic factor (BDNF) inside the neuclei. The increased BDNF can improve neuronal plasticity, resulting in having more axons and dendrites of the neurons through neurogenesis (Shen 2011a).

In a nutshell, the patients with inadequate BDNF have a tendency to cause apoptosis of neurons, showing the evidence of decreased volume in hippocampus, and manifesting clinically with depressive symptoms ; contrariwise, those with nourished neurons after antidepressant therapy show normal mood (Sheline et al., 2003).

Table 1 Classification of antidepressants* based on therapeutic functional consideration

- 5-HT-related antidepressants (SSRIs)
  Effective for part of MDD as well as panic disorder, phobia, OCD, PTSD and acute stress disorder
- Both 5-HT and NE-related antidepressants § (moclobemide, venlafaxine, milnacipran, duloxetine, mirtazapine)
  Effective for part of MDD as well as panic disorder, phobia, OCD, PTSD, acute stress disorder and GAD
- NE-related Antidepressants (bupropion, agomelantine)
  Effective for part of MDD and GAD

* Listed are only those which can be easily prescribed to clinic therapeutic doses
§ Dual-acting antidepressants
SSRIs, selective serotonin reuptake inhibitors ; MDD, major depressive disorder ; 5-HT, serotonin ; OCD, obsessive-compulsive disorder ; PTSD, posttraumatic stress disorder ; GAD, generalized anxiety disorder
Reproduced and expanded from : Shen, 2011a, with permission to reprint from Taipei : Ho-Chi Publishing Company

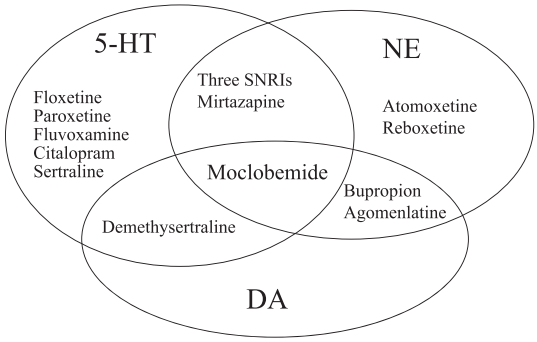

Figure 3 The relationship of three monoamines and commonly used antidepressants. 5-HT, serotonin ; NE, norepinephrine ; DA, dopamine. Three SNRIs, serotonin and norepinephrine reuptake inhibitors (venlafafine, milnacipran, and duloxetine). Reproduced and expanded from : Shen, 2011a, with permission to reprint from Taipei : Ho-Chi Publishing Company

Functional Classification of Antidepressants

The classifications of antidepressant have a couple of systems such as according to chronologic dates of introduction, and chemical structures. But the functional classification is currently most popular and clinically most relevant. In this classification, the only thing counts is the involvement in related monoamines in neurotramsisson — serotonin, norepinephrine, and dopamine. Table 1 lists the functional classification for some commonly heard antidepressants.

In basic neurobiology, clinicians also have some ideas how those three monoamines are related to human mood and behaviors. Figure 3 depicts how the mood and behaviors are related to three monoamines. The experienced psychiatrists can prescribe the clinically appropriate antidepressants for their patients, especially if the patients are comorbid with anxiety disorders or anxiety symptoms.

Patients with phobia, obsessive compulsive symptoms, or panic symptoms, should be prescribed with an antidepressant (an SNRI or an SSRI) with the ability in improving serotonin neurotransmission of the brain. But those antidepressants devoid of improving serotonin neurotransmission (buproprion, or aglomenlatine) should be avoided although bupropion has been shown in decreasing anxiety score in clinical drug trial. On the contrary, patients are better treated with bupropion (Shen, 2011a) or agomenlatine (Stahl, 2014 ; Zajecka et al., 2010) if they present

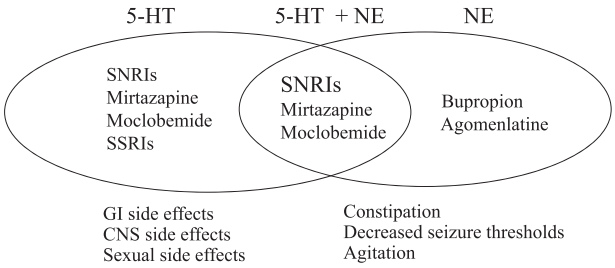

Figure 4 Antidepressants, their transmitted neurotransmitters and side effects. 5-HT, serotonin ; NE, norepinephrine ; SNRIs, serotonin and norepinephrine reuptake inhibitors (venlafaxine, milnacipran, and duloxetine) ; SSRIs, selective serotonin reuptake inhibitors (fluvoxamine, paroxetine, sertraline, fluoxetine, and citalopram ; GI, gastrointestinal ; CNS, central nervous system. Reproduced and expanded from : Shen, 2011a, with permission to reprint from Taipei : Ho-Chi Publishing Company

themselves with lack of energy but without any severe presentation of phobic, OCD, or panic symptoms.

Dual action antidepressants such as SNRIs (venlafaxine — [Allgulander et al., 2001] and duloxetine [Allgulander et al., 2008])— or mirtazapine (Thase, 2010) are the antidepressants of choice if the patients are comorbid with generalized anxiety disorder (APA 2013) or having generalized anxiety symptoms such as excessive worry or muscle tension (Shen, 2011a). Patients with pain symptoms are also better treated with dual action antidepressant such as duloxetine (Goldstein et al., 2005), venlafaxine (Yucel et al., 2005), milnacipran (Derry et al., 2012), or mirtazapine (Christodoulou et al. 2010).

Antidepressants with serotonin transmission have three major side effects — gastrointestinal symptoms (nausea, stomach upset, abdominal discomfort), excitement (difficulty in falling asleep, agitation, vivid dreams), as well as sexual dysfunction (decreased desire, orgasmic inhibition, delayed ejaculation, and difficulty in erection or vasocongestion/lubrication) (Shen, 2011a). The antidepressants with norepinephrine transmission have the side effects of constipation, dryness of the mouth, paraesthenia, nausea, or headache. But all those side effects are easily tolerated by the patients (Shen, 2011a ; Versini et al., 1999). Figure 4 depicts the side effects induced by antidepressants.

Remission as a Goal in Antidepressant Therapy

The term "remission" from depression (Frank et al., 1991) is a term borrowed from the terminology in oncological treatment. In research, criteria for remission from depression are defined as a major depressive disorder patient (A) who has the dropping of Hamilton Depressive Rating Score (Hamilton 1960) down to 7 or below ; (B) who has returned to premorbid functional level, and (C) who can sustain those improved conditions for two months or more (Frank et al., 1991).

In a questionnaire survey on a group of 535 major depressive disorder outpatients in remission after treatment (Zimmerman et al., 2006), those patients from their own perspective have expressed high consistency in four major definitions — (A) having the sense of positive mental health (optimism, vigor, and self-confidence) ; (B) feeling like their usual, normal self ; (C) having general sense of well-being ; and (D) absence of symptoms of depression. With both objective and subjective definitions, the experienced psychiatrists should easily know when their clinic patients are in remission from depression during clinic follow-ups.

"Cure" from depression is a "medical utopia" that is not to be found. Like arthritis, gouty attack, peptic ulcer, etc., depression tends to recur as its natural course of the disease (APA, 2010 ; Frank et al., 1991). Because the favorable outcomes of antidepressant treatment are predictable and sustainable, patients with depression should be frankly explained that they will get remitted soon after the treatment, but the remitted depressed patients should be maintained with the same dosage as used in acute treatment (Frank et al., 1993) at least for 6–9 months (APA, 2010). But the patients should be told clearly that depression tends to have another recurrent episode in the future (Frank et al. 1991) after they stop taking antidepressants.

Maximalization in Antidepresasant Therapy

Anderson et al.'s in 2006 wrote a guideline to help set up the levels of the care for patients with breast cancer for each country in the world according to its financial resources. The levels of care can be classified into basic, limited, enhanced,

and maximalized depending on available resources. Modeling with this guideline, I think that antidepressant therapy for patients with major depressive disorder and anxiety disorders can be maximalized if the clinicians can pay attention to simple principle for antidepressant prescriptions. Clinicians just need to pay more attention to those principles, the effectiveness of patients' antidepressant therapy can be maximalized, but the resources spending in antidepressant therapy are not substantially increased.

Leo E. Hollister (1915–2000) first introduced the concept of four D's (diagnoses, drugs, dosage, and duration) to re-examine patients with treatment-refractory depression (Csernanski and Hollister, 1986). In the section of the overview here, I am also borrowing this concept to explain how to maximalize the antidepressant therapy.

Diagnoses

As stated in the previous section of this review, the symptoms and signs of major depressive disorder consist of nine *DSM* symptoms which are listed according to the frequency of occurrence of those symptoms in MDD patients. The ranking of these symptoms is based on Western patients. But Asian patients are more concerned with eating and sleeping function rather than the first two MDD symptoms — depressive mood and lack of interest.

With *DSM*-based questionnaire, the life time prevalence of major depressive disorder in the communities in Taiwan was 1.1% in 1980s (Hwu et al., 1996), and 1.20% in 2000s (Liao et al., 2012), but the reference number for the life time prevalence for MDD was 5.8% in Epidemiological Catchment Area (Regier et al., 1988), and 17.1% in National Comobidity Survey (Blazer et al., 1994) in the USA. Thus, those *DSM*-based clinical questions can be overlooked if the MDD symptom checking is not carefully done.

The depressed patients with anxiety symptoms requires longer time to get remitted under citalopram therapy than those without anxiety symptoms (Fava et al. 2008), although both groups can eventually get remitted. In the concept of *DSM-5*, the patients with psychotic features are no longer considered as having higher severity and poorer prognosis compared to those without psychotic features. The psychiatrists just need to add small dose of antipsychotic drugs to control the concurrent psychotic symptoms and to make antidepressant effectively work.

Drugs

Some inferior medications such as Buderprion XR®, a generic bupropion was removed by US Food and Drug Administration (*Psychiatric News* October 11, 2012). The antidepressant trazodone has been shown to be not as effective (APA, 2010 ; Goh et al., 2012) as other antidepressants such as bupropion (Weisler et al., 1994) and venlafaxine (Cunningham et al., 1994) in controlled studies.

In the STAR*D study with about 4,000 study patients (Trivedi et al., 2006), the investigators found that only 28% of patients treated with 10–12 weeks of citalopram, an SSRI, at the dosage level of 20–40 mg/day get remitted from depression. In meta-analysis studies, SSRIs as a group are not considered effective in getting MDD patients remitted (Lam et al., 2009) as compared to other dual action antidepressants such as mirtazapine (Thase et al., 2010), or venlafaxine (Thase et al., 2001) or duloxetine (Thase et al., 2007b).

The patients with generalized anxiety disorder have also been found that venlafaxine (Allgulander et al., 2001) or duloxeline (Allgulander et al., 2008) is more likely to get remitted quicker as compared with those GAD patients treated with SSRIs.

Therefore, clinicians should no longer consider all antidepressants as equally effective, and we should choose better dual action antidepressants to maximalize the efficacy of antidepressants.

Doses

In designing rating scales for monitoring the treatment efficacy for depressed patients, citalopram has been found that low dosage level (10–20 mg/day) is not therapeutic in getting patients remitted as compared to a higher dosage level (30–40 mg/day) (Bech et al., 2001).

Table 2 lists minimal daily doses of dual action antidepressants. Clinicians need to be concientious to prescribe adequate antidepressant doses for their depressed patients.

Related to the doses, I would like to mention that patients' initial tolerance to a given antidepressant is also dose-related. In a South Korean study (Lee et al., 2012), the investigators found

Table 2 Minimal daily dosage of dual action antidepressants

Drugs	Minimal daily dosage (mg/day)
Venlafaxine	150
Millacipran	100
Duloxetine	60
Mirtazapine	30
Moclobemide	300

Table 3 Dosage titration for dual action antidepressants is always necessary to avoid their initial side effects (unit＝each pill or capsule)

Antidepressant	Treatment days													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Venlafaxine (75 mg)	¼	¼	½	½	½	1	1	2	2	2	2	2	2	2
Milnacipran (50 mg)	½	½	½	½	1	1	1	2	2	2	2	2	2	2
Duloxetine (30 mg)	1	0	0	1	0	1	1	2	2	2	2	2	2	2
Mirtazapine (30 mg)	⅙	⅙	⅙	½	½	½	1	1	1	1	1	1	1	1
Moclobemide (150 mg)	1	1	2	2	2	2	2	2	2	2	2	2	2	2

that patients have nausea as the major side effect in the first week of receiving duloxetine either with full or empty stomach, but that all patients tolerate the full dosage of duloxetine (60 mg/day) in the second week. Thus, clinicians can use low dose of antidepressant, then titrate up the dose gradually to the full-dose level of an SNRI in about one week to avoid high initial drop-out rate such as in a milnacipran clinical trial in Taiwan (Chang et al., 2008). Mirtazapine is also needed to use smaller dose level in the beginning to improve patients' tolerability for the side effect of sedation. Table 3 is my suggested titration table to help patients tolerate the initial dosing of dual action antidepressants.

The antidepressant-treated patients should be maintained with the same dosage levels of the antidepressant used in the acute treatment. Any dosage reduction of the antidepressants can compromise the efficacy of the maintenance therapy (Frank et al., 1993).

Duration

All antidepressants take a period of two weeks to see appreciable clinical response. Quitkin et al. (1984) found that a significant proportion of patients who showed no clear-cut response at four weeks would show much improvement in antidepressant therapy at six weeks in drug- but not placebo-mediated patients. In diagnostic antidepressant trial, the geriatric depression is expected to wait and see the improved depression in two months.

The patients with milder depressive symptoms may take even seven weeks to see a significant improvement of symptoms compared with normal controls (Judd et al., 2004). Therefore, the clinicians should be aware of the nature of the treatment. A study showed that patients receiving newer antidepressants rather than old tricyclic antidepressants can stay in adequate dosages and adequate durations of the antidepressant therapy (Katon et al., 1992).

In a nutshell, simply paying attention to those four D's (diagnoses, drugs, doses, and duration) prescription principles, the clinicians can easily maximalize the quality of antidepressant therapy for patients with MDD and anxiety disorders. At the same time, remission rate for patients with MDD and anxiety disorders can be substantially achieved without much increased financial burdens or other resources.

Potentiations in Antidepresasant Therapy

Regular and adequate exercise

Besides improvement of monoamine neurotransmission, aerobic exercise, (but not muscle strength training [Goekint et al., 2010]), can increase BDNF levels of the brain (especially, in hippocampus) to enhance neuronal plasticity (Cotman and Berchtold, 2002). In other words, like antidepressant, exercise can promote the brain health through increased levels of BDNF of the brain besides the physical benefit to prevent coronary disease (Glassman et al. 2002) and stroke (Jorge et al., 2003). American Heart Association suggests adequate exercise with (A) at least 150 minutes per week of moderate exercise, or (B) 75 minutes per week of vigorous exercise, or (C) a combination of moderate and vigorous activity. "Thirty minutes a day, five times a week is an easy goal to remember" (www. heart. org/HEARTORG).

Patients under antidepressant therapy need to be instructed to exercise or a least increase physical activity routinely (Stubbs et al., 2016 ; Takeda and Shen 2014) to enhance antidepressant effect. The endocrinologist is considered professionally incompetent if the doctor prescribes only anihyperglycemic drugs without demanding the diabetic patients to control diet. In my opinion, a psychiatrist is liable for malpractice if he/she just prescribes antidepressants to the depressed patients without instructing them to do regular exercise. The depressed patients should continue the habit of regular exercise to help reduce the chance of relapse or recurrence of depression even after antidepressant therapy is discontinued.

Add-on treatment (augmentation therapy) while on an antidepressant

Experienced psychiatrists are familiarized with switching current antidepressant to another antidepressant, or augmenting the dosage of the existing antidepressant if the antidepressant therapy is not optimal (Trivedi et al., 2006). To follow the strategies of four D's approaches carefully as described in the previous section of this review, the antidepressant therapy can be easily maximalized.

Some useful add-on therapies can be prescribed to potentiate the antidepressant efficacy for the depressed patients under antidepressant treatment. The most common add-on therapy is that mirtazapine or bupropion is prescribed on top of existing SSRI/SNRI therapy to rid of the residual symptoms of sleep disturbances or lack of energy, respectively (Shen, 2011a). Some patients do not respond to antidepressant therapy satisfactorily. For those non-responders or partial responders, triiodothyronine (T3, up to 50 μg/day) or lithium (up to 900 mg/day) (Nierenberg et al., 2006) is prescribed. In addition, other agents (such as St. John's Wort, omega-3 fatty acids, etc.) (APA, 2010) are also another add-on drugs or nutritional supplements to the existing antidepressants to potential the antidepressant therapy.

Management of treatment-refractory depression

Even after a careful four D's approach, some depressed patients still cannot get remitted after at least two antidepressant therapies is called "treatment-refractory depression" (Dunner, 2013). For patients with treatment-refractory depression, add-on (augmentation) treatments with one of second-generation antipsychotic drugs — aripiprazole (Berman et al., 2007 ; Chen et al., 2012 ; Kamijima et al., 2013), olanzapine (Thase et al., 2007a), and quetiapine (McIntyre et al., 2007) — have been approved for the indications by regulatory agencies of various countries.

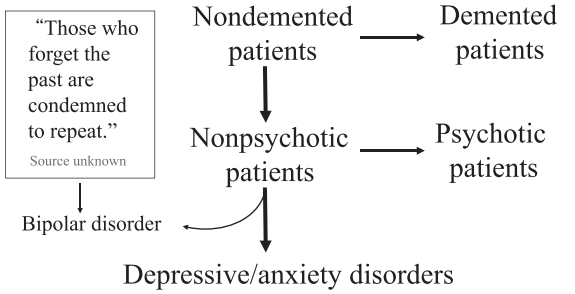

Figure 5 A simple flow chart in making a psychiatric diagnosis. The patient is roughly not dementic if he/she can carry a decent conversation at the psychiatric clinic. The patient is not psychotic if he/she denies any experiences of having hallucinations and delusion. The patient is possibly having depressive/anxiety disorder in the absence of a history of mania. Concept adapted from Goodwin and Guze, 1996.

Table 4 *DSM-5* classifications for antidepressant-medicated disorders

・Depressive disorders
・Anxiety disorders
・Obsessive-compulsive and related disorders
・Trauma-and stress-related disorders
・Sleep-wake disorders
・Feeding and eating disorders

Adapted from American Psychiatric Association : *Diagnostic and Statistical Manual of Mental Disorder, the Fifth Edition* (*DSM-5*) 2013

Managing treatment-refratory depression, psychiatrists need another careful re-assessments for the treatment. Those patients with treatment-refractory treatment may receive neuromodulating techniques such as repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), or vagus nerve stimulation (VNS), etc. (Dunner, 2013).

Antidepressants as Versatile Drugs

Figure 5 shows how the simple logic that depression and anxiety are diagnosed. Unless those patients have a history of manic episodes, their correct medications are most likely antidepressants. A recent report has suggested that the early use of antidepressants would have prevented unneeded suicidal mortality in depressed patients with Alzheimer's disease (Enache et al. 2016).

Beside the indications for depression and anxiety disorders, duloxetine has been indicated for various pain symptoms including peripheral diabetic neuropathy (Goldstein et al., 2005) and stress urinary incontinence (Norton et al. 2002). To note, patients with somatization has been persistently found to have decreased BDNF levels (Kang, et al. 2016).

In fact, antidepressants are also drugs prescribed commonly for diseases of various *DSM-5* (APA, 2013) diagnostic categories (Table 4). Some off-label indications include treatment for weight control (bupropion), restlessness leg syndrome (bupropion), attention deficit/hyperactivity (bupropion or venlafaxine), etc. (Shen, 2011a).

Antidepressant therapy can prolong poststroke patients' survival rates (Jorge et al., 2003). In a randomized, double-blind, placebo-controlled trial conducted in 40 outpatient cardiology centers, sertraline, an SSRI, can help prolong the life in depressed patients with acute myocardial infarc-

tion and unstable angina (Glassman et al. 2002). In a review paper, Evans et al. (2005) suggested that biological mechanisms underlie a bidirectional link between depression and many medical illnesses, and that mood disorders affect the course of medical illnesses, implying that antidepressant treatment help control medical conditions.

"The mind, in addition to medicine, has powers to turn the immune system around." said by Jonas Salk (1914–1995), a polio vaccine inventor. This metaphorical statement quoted by O'Regan in 1986, best describes what antidepressants do for the human body because antidepressant therapy can lower down the cortisol level in the body, resulting in improving body immunity.

In an animal study (Andoh et al., 2002), the investigators found that selegiline, a monoamine oxidase inhibitor, can produce thioredoxin, which has neuroprotective or cytoprotective function to protect the animal's hearts from damage due to excessive oxidative stress.

SSRI has been reported to inhibit the growth of prostate cancer cells (Abdul 1995). In an animal study, mirtazapine has been shown to have stronger anticancer activity than cisplatin (Bilici et al. 2012) or to have anticancer activity through the change in immune environment (Fang et al. 2012). Recently, research interests on anticancer activity from SSRIs and SNRIs have been focused on hepatocellular carcinoma (HepG2) cells and mechanism of apoptosis through activation of caspase (Kuwahara et al., 2015) and the mitogen-activated protein kinase (MAPK) pathways (Chen et al. 2014). Further research are needed to demonstrate whether antidepressants can be used as anticancer drugs in the future.

Drug Lag for Antidepressants in Japan

In a US nationwise survey on psychotropic prescription patterns by outpatient psychiatrists, primary care physicians, and other medical specialists, 62.3% of all prescriptions prescribed belong to antidepressants (Pincus et al. 1998). The investigators also reported that although visits for depression were doubled for both psychiatrists and primary care physicians, antidepressant prescriptions were mostly increased by psychiatrists but not for primary care physicians. To note, the membership number of the American Psychiatric Association is about 37,000 for the population of 320 million in the US (Moron et al. 2017).

A 2010 report (Marcus and Olfson, 2010) showed that the clinic visits for depression patients in the US were about 2.88 per 100 total national clinic patient visits in 2007. The investigators also found that rapid increases in depression treatment from 1987 to 1997 were followed by more modest increases during the following decade, but that there was little change in the proportion of patients receiving antidepressants, treatment with psychotherapy has declined. The annual volume of total antidepressant sales in 2011 in the US was at US$12 billion, which was roughly the same output of American total movie industry (Verison VONA 2011). Antidepressant prescriptions had been remarkably increased in two decades (1980's and 1990's) co-incidentally after SSRIs were introduced to the US market.

In Japan, the number of antidepressant prescription in 1980's and 1990's was significantly less (Kanba 1999). A study (Shimazawa et al., 2012) showed that only 13 psychiatric drugs were introduced in Japan between September 2000 and July 2011 among 23 standard psychiatric drugs which were approved in the USA and the UK. The median review time (from approval application to approval) of those 13 drugs in Japan was 23 months, which was considerably longer than those of the US Food and Drug Administration and European Medicines Agency (10.0 and 13.5 months, respectively). The biggest barrier to antidepressants coming to the market is that the medical insurance system in Japan is national, and the authorities were containing a potentially explosive market for antidepressants (Berger and Fukunishi, 1996 ; Berger 2005).

Conclusion

Despite the indications of antidepressants are many for various diseases, the use of antidepressant is quite disappointing in various countries (Thornicroft et al., 2017). In 1990's and 2000's, the prescriptions for antidepressants in Japan were problematic because many popular post-TCA antidepressants were not available on Japanese market. Many foreigners in Japan at that time lamented about the inconvenience while living in Japan (Schulz 2004). Hill, a foreign author, said exclamatorily that Japan in 2006 was one of the most advanced countries in the world, but Japan just gave the worse substandard treatment for depression for her people. Later, the problems of drug lags of antidepressants in Japan (Berger 2005 ; Kanba 1999) have been little by little improved in clinical drug trials in Japan and introducing international agreement to make the

Table 5 Post-tricyclic antidepressants in Japan

SSRIs
Fluvoxamine (Luvox®, Depromel®)
Sertraline (J Zoloft®)
Paroxetine (Paxil®)
Escitalopram (Lexapro®)
SNRIs
Milnacipram (Toledomin®)
Duloxetine (Cymbalta®)
Venlafaxine (Effexor®)
Others
Trazodone (Desyrel®, Reslin®)
Mirtazapine (Remeron®, Reflex®)

SSRIs, specific serotonin reuptake inhibitors ; SNRIs, norepinephrine and serotonin reuptake inhibitors

results of drug trials reciprocal among participating countries (Berger and Fukunishi, 1996).

Along with the new antidepressants introduced in Japan in the past two decades, heavy industrial promotion has accompanied the campaign of awareness for depression in Japan. The term changes of depression in Japan from *utsubyo*, which is conveyed to the patients as *ki ga fusagu, ki ga omoi,* or *ki ga meiru* to "the cold of the heart" *(kokoro no kaze)* have helped promote tremendously the sale of antidepressants in Japan (Schulz, 2004).

In Japan, the symptom of the circulation system for depression was metaphorical as "the heart being disturbed" *(kokoro midarete),* as in famous 1969 Nagata Takashi's song *In Nagasagi, Today Also Already Rained*. But this original heart-related meaning has suddenly been twisted to *chi*-related respiratory symptom through introducing *kokoro no kaze* for effective antidepressant promotion. Table 5 lists available non-tricyclic antidepressants in Japan. Antidepressants in Japan cover almost most important categories of the drugs necessary for a psychiatric practice although the list is not exactly complete as compared to those in the US.

The membership of 16,000 psychiatrists of the Japanese Society of Psychiatry and Neurology (Shinfuku, 2012) are serving the Japanese population of about 127 million. The ratio of psychiatrists to the population in Japan is 12.4 per 100,000. The ratio of psychiatrists to the population in the US is 11.5 per 100,000 (37,000/321 million). Two numbers of ratios in those two countries are similar, or a little bit better favoring for Japanese psychiatrist manpower. Therefore, the antidepressant prescriptions are expected to be continuously increased in Japan if Japanese psychiatrists keep prescribing antidepressants for those suffer from depression. Also thanks for the campaign of *kokoro no kaze,* the notorious high suicidal rate in Japan is expected to decline through the popular use of antidepressant therapy in the near future (Bostwick et al., 2016 ; *The Japan Times*, May 31, 2016). *Ganbatte!*

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The readers are warned that this article contains some information of off-label use of antidepressants. The physicians should consult with the package inserts and check the dosage levels of antidepressant before prescribing antidepressants to their patients. The opinions expressed here are the author's personal opinions, which are unnecessarily reflected on those of his hospital or university.

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