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Cognitive-Behavioural Therapy Combined with Antidepressants for Major Depressive Disorder

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1. Introduction

Major depressive disorder (MDD) is a common psychiatric illness. Its 1-year prevalence rates varied in the different regions, for instance 5.1% in Australia, 6.7% in New Zealand, 5.8% in Netherlands, 7.1% in Hungary, 6.2 in Italy, 15-23 % in Republic region of Udmurtia (rural area), 3.5%-10.3% in USA and 4.1%-4.6% in Canada (Handerson et al., 2000; Oakley-Browne et al., 1989; Pakriev et al., 1998; Bijl et al., 1998; Szadoczky et al., 1998; Faravelli et al., 1990; Bourdon et al., 1992; Offord et al., 1996; Bland et al., 1988). However, its prevalence in Taiwan is in a lower range of 0.6%-1.1% (Hwu et al., 1989). According to a meta-analysis of 11 clinical studies, the mean average of its 1-year prevalence rate is 4.1% (95%CI, 2.4% to 6.2%), and its sex-specific 1-year prevalence rates for men and women are 4.9% (95%CI, 3.3% to 7.1%) and 10.0% (95%CI, 6.4% to 14.6%) respectively (Waraich et al., 2004). The lifetime prevalence for MDD patients is 12.6% in New Zealand, 15.4% in Netherlands, 15.1% in Hungary, 13.1% in Italy, 15.7%-22.8% in Switzerland, 9.0% in Germany, 5.9%-17.1% in USA and 8.6%-29.6% in Canada (Oakley-Browne et al., 1989; Bijl et al., 1998; Szadoczky et al., 1998, Carta et al., 1995; Wacker et al.1992; Wittchen et al., 1992 ; Kessler et al., 1994; Bourdon et al., 1992; Murphy et al., 2000; Fournier et al. 1997; Bland et al., 1988). For Asian countries, the prevalence is 1.9% in Hon Kong, 3.4% in Korea and 0.88%-1.7% in Taiwan (Chen et al., 1993; Lee et al., 1987; Hwu et al., 1989). Its prevalence in Puerto Rico is 4.6% (Canino et al., 1987). A meta-analyis of data obtained from several countries revealed that its lifetime prevalence is approximate 3.8% (95%CI, 2.4% to 23.1%) for men and 7.5% (95%CI, 4.5% to 11.3%) for women (Waraich P, 2004).

Depression is associated with various chronic medical conditions, including cardiovascular disease, hypertension, diabetes, arthritis and back pain. Recent evidence suggested that it is a primary risk factor for coronary heart disease (CHD), including myocardial infarction (MI) and cardiac death (Lett et al., 2004; Rugulies, 2002). In the contrary, patients with myocardial infarction (MI) and cardiac death also have an increased risk of depression. Depression is also associated with hypertension (Patten, 2001; DiMatteo et al., 2002). Despite of the heterogeneity of results, depression was found to be a risk of poor adherence to antihypertensive medications (Eze-Nliam et al., 2010).

Diabetic patients also have a high risk for depression. A systemic review has found that diabetes doubles the odds of comorbid depression (Anderson et al., 2001) and increases the risk for depression for 24% (Nouwen et al., 2010). In the contrary, depression also increases the risk of diabetes development. In addition, depression has been associated with

hyperglycemia, diabetic complications, functional disability and mortality among diabetic patients (Rustad et al., 2011).

The relationship of arthritis and depression has been well documented. A recent study has shown a strong association of depression and functional severity of rheumatoid arthritis (RA) and its related diseases (Godha et al., 2010). Another study also suggested that depression is highly correlated with the disease activity of rheumatoid arthritis (RA), especially the number of swollen joints and joint functional class (Khongsaengdao et al., 2000).

Depression is a major burden for individuals, communities and health services throughout the world. The study of global burden of diseases in the year 2000 indicates that depression is an important causes of disease burden accounting for 4.4% of total disability adjusted life years (DALYs) in the year 2000, which is almost 12% of all total years lived with disability worldwide (Ustün et al., 2004). Effective pharmacological and psychosocial interventions to resolve depressive symptoms promptly could be reduce this burden.

Pharmacotherapy, psychotherapy and their combinations are effective treatment for MDD. Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) are examples of medications approved for the treatment of MDD. Examples of effective psychotherapy techniques are cognitive therapy (CT), cognitive behavioural therapy (CBT), interpersonal therapy (IT) and mindfulness-based cognitive therapy (MBCT). Although most patients respond to these interventions, a considerable proportion of them may not respond or only partially respond to them. Combined psychotherapy and pharmacotherapy is therefore a choice for the latter group of patients.

The aim of this chapter is to summarize the efficacy and safety of CBT combined with antidepressants. However, the efficacy and safety of antidepressants alone and CBT alone are also addressed.

2. Cognitive behavioral therapy

2.1 Cognitive model of depression

The cognitive model of depression is supported by several research findings. The cognitive theory addressed in several studies comprises of three components: cognitive triad in depression, negatively biased cognitive processing of stimuli and identifiable dysfunctional beliefs (Beck, 2005).

The components of cognitive triad include the patterns of depressed patients interpreting experiences, viewing themselves and viewing future in a negative way. The first triad is the negative interpretation of experience. Persistently, depressed patients tend to interpret the interaction between themselves and environment as representation of defeat, deprivation and disparagement. They perceive that their lives are plentiful of burdens, obstacle and traumatic events. The second triad is the negative evaluation of the self. Patients view themselves as deficiency, inadequacy and worthlessness. They tend to regard themselves as having a physical, mental or moral defect. They usually reject themselves because of those unpleasant defects. The last triad is the negative expectation of future. Depressed patients assume that the current difficulties and suffering will last forever. Their lives have endless obstacles, frustration and deprivation. These cognitive distortions are cause of depression (Beck, 1967).

There are some of common maintenance processes in the depressed patients. The vicious cycle linking a depressed mood with cognitive bias, and negative appraisal causes the negative view of self, then maintaining the depressive symptoms. The negative appraisals

and depressive symptoms could reduce depressed patients' activities usually providing the pleasure and sense of achievement for them, and thus the decreased activities continue the depression. The symptoms of depression and negative appraisal may decrease the ability to cope and deal with their difficulties. They may feel hopelessness and continue to be depressed (Wrestbrook et al. 2007).

2.2 Cognitive behavioral therapy for depression

CBT is a collaborative, short-term, structured, focused approach psychotherapeutic intervention. The aims of CBT are to help the patients to understand the relationship of cognitions, emotions or affect, behaviours and physiology influenced by external stimuli. In addition, it would educate the patients on two-way relationship between cognition and behaviour in which cognitive processes can influence behavioural patterns, and behavioural changes can influence cognition (Wright, 2006).

For the treatment of depression, CBT allows to use several techniques. In the early phase of treatment, the behavioural technique such as exercise or activity scheduling is used to reduce the depressive symptoms. For instance, high level physical exercise appears to be effective in reducing the depressive symptoms, and behavioural activities could prevent the reduction of activity in depressed patients. Then, the early cognitive technique is used to distract the patients from their negative automatic thoughts (NATs) and/or to change the attitude toward them. Some depressive symptoms may be relieved or reduced. The last, main cognitive behavioural technique is applied. In this phase, the patients learn to identify the NATs and alternative thoughts, self monitoring, thought records or behavioural experiment to disconfirm their NATs and to prove alternative hypothesis. In addition, the therapist also teaches the depressed patient to use the problem solving skills to reduce the depressive symptoms and risk of suicide (Wrestbrook et al. 2007).

Besides the treatment of depression, CBT is widely used for several mental health conditions, e.g. anxiety disorders, personality disorders, eating disorders and substance use disorders (Beltman et al., 2010; Hofmann & Smits, 2008; Linehan et al., 1991; Fairburn et al., 1995; Magill et al., 2009). CBT adjunct with medications is also beneficial for schizophrenia and bipolar disorder (Turkington et al., 2004; da Costa et al., 2010).

3. Treatment for major depressive disorder

3.1 Short-term treatment (acute phase) (6-12 weeks)

In this phase, the patient experiences severe symptoms of depression. The goal is to relieve those symptoms. Most patients turn to be a remission at the end of this phase.

3.1.1 Antidepressants

There have been several randomized-controlled trials and meta-analyses comparing the efficacy and tolerability of antidepressants among MDD patients. While the efficacy of most antidepressants is relatively comparable, their tolerability appears to be varied based on their mechanisms of action.

3.1.1.1 Tricyclic antidepressants

3.1.1.1.1 Tricyclic antidepressants vs. Placebo

Several systemic reviews demonstrated the efficacy of tricyclic antidepressants (TCAs) for MDD. In a meta-analysis of 32 placebo-controlled trials with 4314 patients, Storosum et al.

(2001), compared the short-term efficacy of TCAs with placebo. Their results suggested that TCAs are effective in the short-term treatment of MDD. Another meta-analysis of Furukawa et al. (2003, 2002) including 35 studies (2013 participants) compared low-dose TCAs (75-100 mg/day) withplacebo for the treatment of depression. The findings suggested that low dose TCAs is superior to placebo in term of response rates while the tolerability of those TCAs is not significantly different from placebo.

Although several lines of evidence support that TCAs is effective for adult depression, their efficacy for depression in children and adolescents is still controversial. A meta-analysis of Hazell et al. (1995) reviewed 12 randomised controlled trials comparing the efficacy of tricyclic antidepressants with placebo in depressed children and adolescents. The review showed that TCAs might not be effective for the treatment of depression in this age group. Another meta-analysis of TCAs for depressive disorders in children and adolescents including nine randomized, placebo-controlled trials supports the earlier findings (Maneeton et al., 2000).

3.1.1.1.2 Tricyclic antidepressants vs. selective serotonin reuptake inhibitors

Several systemic reviews compared TCAs with SSRIs in the treatment of MDD. A meta-analysis of efficacy and tolerability in hospitalized depressed patients suggested that some TCAs, in particular amitriptyline, may be superior to SSRIs. A dual action of both 5-HT and noradrenaline reuptake inhibitors of those TCAs may be a possible explanation for the superiority. However, the meta-analysis found that SSRIs had a modest advantage in terms of tolerability (Anderson 1998, 2000).

In the contrary, a few systemic reviews found no superiority of TCAs over SSRIs. A meta-analysis of 11 studies including 2,951 participants comparing SSRIs with TCAs in the treatment of depression showed that their efficacy were comparable but the TCA patients dropped out more frequently. Another meta-analysis of 181 randomized clinical trials (47% were inpatients, and 53% were outpatients), compared amitriptyline with SSRIs (Barbui et al., 2004). Amitriptyline therapy was not superior to SSRIs in both outpatients and inpatients.

A meta-analysis of Arroll et al. (2005) reviewed ten studies of TCAs and SSRIs as comparison to placebo for treatment of depression in primary care. One half of those studies were at low methodological quality, and nearly all studies were short-term trials (six to eight weeks). The review showed that TCAs and SSRIs are more effective than placebo. In addition, the efficacy of low-dose and high-dose TCAs is comparable.

TCAs may be less tolerable than SSRIs. A meta-analysis of Anderson et al. (2000) reviewed 62 randomized controlled trials including 6,029 patients with MDD comparing SSRIs with TCAs in term of treatment discontinuation. Most study durations of included trials were between four and eight weeks. The analysis showed that the discontinuation rate due to side effect but that not due to treatment failure was more in the TCA-treated patients. Another meta-analysis of randomized, controlled trials also revealed that the overall discontinuation rates of tricyclic/heterocyclic antidepressants were greater than those of SSRIs (Hotopf, et al., 1997). Another meta-analysis of Montgomery (2001) examined the efficacy and tolerability of paroxetine (n = 1924) and tricyclic antidepressants (TCAs; n = 1693) in the treatment of major depression, it included studies from 39 randomized, double-blind, parallel-group studies. The durations of all included studies were six weeks or less. The findings indicated that paroxetine and TCAs have comparable efficacy, but paroxetine is more tolerable. In addition, a meta-analysis of Montgomery et al. (1994) examined 42

published randomized controlled studies also shows a lower discontinuation rate due to side effects as compared with TCAs.

From those reviews, most TCAs and SSRIs are effective in the treatment of MDD. The superiority of amitriptyline to SSRIs is still controversial. As compared with SSRIs, the adverse effects of TCAs are more common and severe. Low dose TCAs should be considered in depressed patients intolerable to the moderate and high doses.

Numerous systemic reviews are conducted to summarize the efficacy and tolerability of SSRIs in treating elderly patients with depression. A meta-analysis of Dunbar (1995) including ten studies carried out in elderly depressed patients demonstrated that paroxetine is as effective as other agents (amitriptyline, clomipramine, doxepin, mianserin). However, the adverse effects of paroxetine might be less frequent and less. These findings suggested that paroxetine might be an alternative first-line treatment to elderly depressed patients.

3.1.1.1.2 Tricyclic antidepressants vs. serotonin norepinephrine reuptake inhibitors

Only few systemic reviews compared TCAs with serotonin norepinephrine reuptake inhibitors (SNRIs). A meta-analysis of van den Broek et al. (2009) compared venlafaxine and TCAs (imipramine, clomipramine, amitriptyline, nortriptyline and desipramine). The average doses of venlafaxine and TCAs were 103.5 and 106.1 mg/day respectively. This review did not find any significant difference of efficacy and tolerability between groups.

3.1.1.2 Selective serotonin reuptake inhibitors

Several systemic reviews have indicated that SSRIs are effective for MDD. In meta-analysis of Bech & Cialdella (1992), citalopram was more effective and more tolerable than placebo. Its dose of 20 mg/day may be enough for patients with mild depression or first depressive episode. However, 40 mg/day may be needed for those with severe or recurrent depression (Montgomery et al., 1994). Another meta-analysis of Tignol et al. (1992) reviewed 178 patients treated with paroxetine and 66 patients treated with placebo and suggested that paroxetine is superior to placebo in the treatment of melancholic depression.

Very few systemic reviews examined efficacy, safety and tolerability of SSRIs in depressed children and adolescents. A systemic review of published and unpublished randomised controlled trials comparing the efficacy and adverse events of SSRIs with placebo suggested that only fluoxetine therapy is effective. However the adverse events and risk of suicidal ideation and behaviour were increased the SSRIs-treated group (Hetrick et al., 2007). The meta-analyses of Whittington et al. (2004) and Usala et al. (2008) also supported the previous review.

From several reviews, SSRIs is effective and acceptable in the treatment of MDD. However, in children and adolescents, fluoxetine may be the only one effective in this population. Since SSRIs have adverse effects and may increase the suicide risk, the use of them in this age group should carefully balance between the risk and its benefits.

3.1.1.3 Serotonin norepinephrine reuptake inhibitors

3.1.1.3.1 Serotonin norepinephrine reuptake inhibitors vs. Placebo

Several systemic reviews have summarized the efficacy and acceptability of serotonin norepinephrine reuptake inhibitors (SNRIs) as comparison with placebo. A meta-analysis of six comparable double-blind placebo-controlled studies comparing venlafaxine with placebo indicated that it is effective for depression regardless of age, gender, presence of melancholia, and severity or duration of depression (Entsuah et al., 1995). In addition,

another meta-analysis also showed that venlafaxine is superior to placebo in reducing symptoms of anxiety in depressed patients (Rudolph et al., 1998).

Desvenlafaxine is another SNRI that is effective, safe and well tolerated for patients with MDD. A pooled study of two studies showed that, after eight weeks of treatment, it is superior to placebo in the treatment of MDD. Its adverse effects are comparable to placebo (Lieberman et al., 2008). Another review of nine studies also demonstrated its short-term efficacy for MDD (Thase et al., 2009). Another meta-analysis of eight clinical trials suggested that desvenlafaxine could improve the functioning and well-being among MDD patients (Soares et al., 2009).

Several reviews have suggested that duloxetine at the doses of 40-60 mg/day is safe and effective in acute phase treatment of MDD (Mallinckrodt et al., 2006). A meta-analysis of Mallinckrodt et al. (2005) reviewed eight double-blind, placebo-controlled clinical trials for up to nine weeks of treatment indicated that duloxetine was superior to placebo in the treatment of depressive disorder both melancholic and non-melancholic types. Another review of two 9-week trials, also demonstrated that duloxetine, as comparison to placebo, has a greater response rate at week two and a greater remission rate at week 5 (Hirschfeld et al., 2005). In addition, the significant difference of efficacy between male and female is not found (Kornstein et al., 2006).

In comparison to venlafaxine, duloxetine may be less effective in the treatment of MDD. There is a systemic review of eight trials, including 1754 patients for efficacy and 791 patients for discontinuation/safety, to compare the efficacy and safety of extended-release (XR) venlafaxine and duloxetine in treating MDD (Vis et al., 2005). The results showed that remission and response rates of venlafaxine were significantly greater than those of placebo and duloxetine. However the adverse events of both drugs are comparable. Another meta-regression analysis also indicated that duloxetine appears to be less effective than venlafaxine in acute phase treatment of adult patients with MDD (Eckert & Lançon, 2006).

From previous reviews, SNRIs are effective for MDD, with comparable tolerability to placebo. However, venlafaxine may be more effective than duloxetine. Venlafaxine, therefore, may be beneficial in patients with severe depressive symptoms.

3.1.1.3.2 Serotonin norepinephrine reuptake inhibitors vs. Selective serotonin reuptake inhibitors

Some reviews compared the efficacy between venlafaxine and SSRIs. Remission rate of MDD during venlafaxine treatment appear to be superior to SSRIs and placebo. A meta-analysis of Thase et al. (2001) compared the remission rate in MDD of venlafaxine with SSRIs/placebo. The study showed that remission rate for venlafaxine is 45 %, while SSRIs and placebo are 35% and 25% respectively. The difference between venlafaxine and SSRIs appear to be significantly different at week 2 while the difference between SSRIs and placebo is significantly different at week 4. Another meta-analysis of eight double-blind, active-controlled, randomized clinical trials also demonstrated that the remission rate of venlafaxine in the treatment of MDD is higher than that of SSRIs (remission rate at week 8: venlafaxine, 40%-55% vs. SSRI, 31%-37%). The recent systemic review of remission between venlafaxine and SSRIs also supports those of findings (Nemeroff et al., 2008).

Another systemic review of 32 double-blind, randomized, controlled trials compared venlafaxine with other antidepressants in the treatment of depression. Its findings indicated that venlafaxine was superior to SSRIs (Smith et al., 2002). Another meta-analysis of five six-week, double-blind, randomized studies including 1,454 outpatients with major depression from comparing the efficacy of venlafaxine with fluoxetine showed that venlafaxine was not

only superior to but also had a more rapid onset of action than fluoxetine (Davidson et al., 2002). The rapid onset of remission for venlafaxine treatment over SSRIs does not differ in age or gender (Entsuah et al., 2001). A recent systemic review comparing venlafaxine and TCAs or SSRIs in MDD also supports the previous reviews (Bauer et al., 2009). The findings showed that venlafaxine might be more effective than SSRIs, and at least as effective as TCAs, for the treatment of MDD and treatment-resistant depression.

Not all systematic reviews support the greater efficacy of venlafaxine over SSRIs. A meta-analysis of 17 trials summarized the remission, response and discontinuation rates between venlafaxine and SSRIs. The results demonstrated that a remission rate of venlafaxine is not superior to SSRIs, while response rate is only small significant over SSRIs (Weinmann et al., 2008).

Although venlafaxine may provide a highly effective antidepressant property, it tends to be associated with high blood pressure. A meta-analysis of venlafaxine affecting blood pressure summarized the results of controlled clinical trials including 3744 patients with major depression. The findings indicated that venlafaxine had a dose-dependent effect on supine diastolic blood pressure (Thase, 1998). Venalfaxine, therefore, may be avoided in depressed patients with hypertension.

There are a few systemic reviews comparing the efficacy of duloxetine and SSRIs in the treatment of MDD. In a meta-analysis, duloxetine showed its comparable efficacy in the treatment of MDD patients as compared with SSRIs. However, its remission rates among patients with moderate to severe depression appears to be higher (Thase et al., 2007).

Milnacipran is another SNRI effective for MDD. A meta-analysis of Puech et al. (1997) reviewed controlled trials comparing milnacipran with imipramine or SSRIs in MDD patients. The study findings showed that milnacipran was as effective as imipramine and might be superior to SSRIs. Milnacipran is as tolerable as SSIRS but more tolerable than TCAs in terms of general and cardiovascular side effects. Another meta-analysis of six studies including 1,082 outpatients with MDD compared the response rates between milnacipran and SSRIs (Papakostas & Fava 2007). The findings suggested that, for the treatment of MDD, milnacipran is as effective as SSRIs.

From those reviews, SNRIs may be as effective as TCAs in the treatment of MDD. Their tolerability and safety are comparable to SSRIs. Venlafaxine and milnacipran may be superior to SSRIs in the treatment of MDD. However venlafaxine is associated with high blood pressure.

3.1.1.4 Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) are a class of antidepressants. They appear particularly effective for atypical depression. There is a meta-analysis of eight studies comparing MAOIs with other antidepressants or placebo in the treatment of atypical depression. Most clinical trials were conducted on reversible MAOIs. The findings showed that MAOIs might be superior to TCA in the treating of MDD with atypical features (Henkel et al., 2006).

Moclobemide, a reversible Inhibitor of MAO-A, have shown its efficacy in treating MDD in many trials. A meta-analysis, as compared with other antidepressants, moclobemide, imipramine, and clomipramine therapies may lead to a higher response rate in patients with depression (Angst et al., 1993). Another meta-analysis of 12 trials including 1,207 outpatients with MDD also showed that efficacy of moclobimide is comparable to that of SSRIs

(Papakostas & Fava, 2006). However SSRIs therapy might have greater rates of nausea, headaches, and treatment-emergent anxiety than that of moclobemide.
From those reviews, MAOIs are effective for atypical depression. The evidences suggest that only moclobimide is as effective as TCAs and SSRIs for the treatment of MDD.

3.1.1.5 Other antidepressants

3.1.1.5.1 Escitalopram

Escitalopram is effective in the treatment of MDD. A previous meta-analysis showed that, after six weeks of treatment, escitalopram was superior to placebo and comparable to TCAs. However escitalopram had fewer adverse events than those of TCAs (Bech & Cialdella, 1992). A systemic review of four studies carried out in primary care settings also demonstrated that remission and response rates of escitalopram were superior to placebo and citalopram, but not venlafaxine-XR. However, its side effects are comparable with other antidepressants (Einarson, 2004). Another meta-analysis of ten clinical trials involving 2,687 patients also supported the previous review results. The findings showed that escitalopram might be superior to SSRIs and comparable to venlafaxine in the treatment of patients with MDD (Kennedy et al., 2006).The results of a recently meta-analysis in eight-week treatment trials of MDD indicated that escitalopram (10-20 mg/day) is superior to and more tolerable than duloxetine (60 mg/day) (Lam et al., 2008). Another systemic review involving clinical trials of escitalopram versus SNRIs (two trials with duloxetine and two with venlafaxine extended release) in outpatients (18-85 years of age) with moderate-to-severe MDD summarized that, over the eight week treatment period, escitalopram was as effective as but more tolerable than SNRIs (venlafaxine XR and duloxetine) (Kornstein et al., 2009). In addition, two meta-analyses showed that the efficacy and tolerability of escitalopram was superior to SSRIs and SNRIs (Kennedy et al., 2009; Lam et al., 2010). Escitalopram may also have a more rapid onset of action than other antidepressants (Kasper et al., 2006).The minimal effective dose for depression is 20 mg/day. However patients with severe or recurrent depression tend to respond to its higher dose (40 mg/day), and less severe depression may respond to its minimal effective dose (20 mg/day) (Montgomery et al., 1994). However, recent meta-analysis findings indicated that the effective doses of escitalopram may be lower than those in previous reviews. The recent review showed that the optimal dose of escitalopram in the treatment of moderate DSM-IV MDD is 10 mg/day, while the effective dose of escitalopram in patients with moderate to severe depression is 20 mg/day.
According to several review findings, escitalopram is effective for MDD. Its efficacy may be greater than that of SSRIs. With a more tolerable profile, it appears to be superior TCAs and SNRIs. The dose range for moderate depression is 10-20 mg/day and for moderate to severe depression is 20-40 mg/day.

3.1.1.5.2 Mirtazapine

A number of systemic reviews have summarized the efficacy and safety of mirtazpine for MDD. A meta-analysis of four clinical studies comparing mirtazapine with amitriptyline and placebo suggested that mirtazapine was as effective as amitriptyline in the treatment of MDD. However, mirtazapine was better tolerated than amitriptyline with respect to adverse events, particularly anticholinergic and cardiac side effects (Stahl et al., 1997). Another meta-analysis including 405 patients demonstrated that mirtazapine and amitriptyline were equally effective for severely depressed patients (Kasper et al., 1997). A systemic review of eight studies also showed that mirtazapine might be superior to placebo and comparable to

amitriptyline for patients with MDD predominant with anxiety/agitation or anxiety/somatisation symptoms (Fawcett & Barkin, 1998). In comparison to SSRIs, a systemic review of ten clinical trials including 1,904 outpatients with MDD showed that mirtazapine and SSRIs were equally effective, but mirtazapine had a preferable side effect profile (Papakostas, et al., 2008). In addition, a meta-analysis of 14 studies involving 1,108 patients with MDD, mirtrazapine appears to have lesser sexual dysfunction than SSRIs (Chen et al., 2008). A meta-analysis of remission rates and time to remission of 15 six-week, clinical trials of mirtazapine and SSRIs showed a higher remission rates in mirtazapine-treated patients after 1, 2, 3, 4 and 6 weeks of treatment. Mirtazapine may have a more rapid onset of action than SSRIs (Thase et al., 2010).
With regard to those reviews, mirtazapine is as effective as amitriptyline and may be superior to SSRIs in the treatment of MDD. The side effect profile of mirtazapine appears to be different from those of amitriptyline and SSRIs.

3.1.1.5.3 Bupropion

Several systemic reviews supported the efficacy, safety and tolerability of bupropion. In a pooled study of clinical studies in MDD patients, at week 8 or end point, bupropion and SSRIs were equally effective and tolerable (Thase et al., 2005). In another meta-analysis of summarized that bupropion XL had a better sexual tolerability than that of escitalopram with similar antidepressant efficacy (Clayton et al., 2006). A systemic review of six clinical trials in MDD patients indicated that bupropion had a greater resolution of sleepiness and fatigue than SSRIs treatment (Papakostas et al., 2006).
From those reviews, bupropion is an effective and tolerable antidepressant. Patients treated with bupropion appear to have less sexual dysfunction than those with SSRIs. It is also beneficial for sleepy and fatigue patients.

3.1.1.5.4 Trazodone

A meta-analysis summarized the efficacy, safety and tolerability of trazodone. Trazodone was compared with imipramine in six treatment studies of depression. The findings suggested that both active drugs were equally efficacious (Patten, 1992). A meta-analysis of nine studies including 988 patients showed that trazodone might be comparable to nefazodone and SSRIs (Papakostas & Fava, 2007). From two review, trazodone seems to be equi-effective and –tolerable as other antidepressants in the treatment of depression.

3.1.1.5.5 Agomelatine

Agomelatine, melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist, is indicated for the treatment of adult MDD. Most clinical trial results supported it efficacy in general depressed patients. A meta-analysis of three clinical studies also suggested that 25-50 mg/day of agomelatine was also effective for severe depression.

3.1.2 Cognitive-behavioural therapy

CBT is effective for MDD. A meta-analysis of four short-term, randomized trials comparing antidepressants and CBT in severely depressed outpatients showed that CBT was as effective as antidepressants (DeRubeis et al., 1999). In comparison to psychodynamic psychotherapy, included studies with at least 13 therapy sessions and a at least 20 patients per group. The review findings suggested that short-term psychodynamic psychotherapy and CBT or behavioural therapy have similar remission or improvement judged by the

patients (Leichsenring, 2001). Another meta-analysis of Beltman (2010) including 29 studies found the effectiveness of CBT for the reduction of depressive symptoms in depressed patients with a diversity of somatic diseases.

In addition, a meta-analysis comparing found that CBT, behavioral therapy, and psychodynamic therapy seem to be superior to pharmacological treatment in elderly depressed patients. However, those nondrug and antidepressant therapies are comparable in treatment those depressed patients (Gerson et al., 1999). There is a systemic review of 57 controlled trials to assess the effects of psychotherapy and other behavioral interventions in depressed older patients. About 19% of the participants discontinued their treatment, with the higher discontinuation rates in group therapies and in longer therapies. The reviews summarized that CBT and reminiscence seemed to be effective and acceptable for older patients with depression. Seven to twelve sessions appear to optimize effectiveness and minimize dropout rates (Pinquart et al., 2007).

Several reviews have shown the efficacy of CBT in patients with depression. Its efficacy for the treatment of depression is comparable to that of antidepressants and other psychotherapy such as short-term psychodynamic psychotherapy. CBT may be beneficial or an alternative treatment for children, adolescents and elderly patients intolerable to antidepressants.

Several reviews have shown that CBT is effective for depression in children and adolescents. A meta-analysis of six randomized trials compared the efficacy of CBT with inactive interventions in depressed patients aged between 8 and 19 years. Most included trials are based on relatively mild cases of depression and moderate quality. The review suggested that CBT may be beneficial for the treatment of depressive disorder with moderate severity in children and adolescents but not recommended for severe depression (Harrington et al., 1998). Another meta-analysis also demonstrated that CBT appears to be effective for depressed adolescents (Lewinsohn & Clarke, 1999; Klein et al., 2007). Since there is a limitation for antidepressant use in children and adolescents, CBT may be an alternative and effective treatment of those patients with MDD.

Although some clinical studies and reviews showed the efficacy of CBT in treating depressed patients, an overestimation of its efficacy from each study may not be overlooked. In a meta-analysis of Cuijpers et al. (2010) examined the effect sizes of 117 studies with 175 comparisons between psychotherapy and control conditions demonstrated that the benefits of psychotherapy for adult depression appeared to be overestimated considerably due to publication bias.

3.1.3 Cognitive-behavioural therapy combined with antidepressants

Although antidepressant or CBT therapy alone shows its efficacy for MDD, significant proportion patients, particular those with severe or recurrent MDD, do not or partially respond to either monotherapy. Combined treatment is, therefore, a choice to raise the response and remission rates. Although many types of combined therapy for MDD are available, psychotherapy, particularly CBT, combined with antidepressants is effective and possibly less adverse effects than other combinations, e.g., combination of two antidepressants. The effectiveness of CBT combined with antidepressant is widely reported. A systemic review of 18 studies including 1,838 subjects receiving psychological treatment alone or combined treatment consisting of the same psychological treatment plus an antidepressant. The review showed that combined treatment is more effective than psychological treatment alone (Cuijpers et al., 2009). However the advantage of combination

appears to be less when an antidepressant is added to CBT (Cuijpers et al., 2009). The clinical study of Thompson et al. (2001) compared the efficacy of desipramine-alone, CBT-alone and their combination for elderly outpatients with depression. The findings indicated that the combined therapy might be effective for severely depressed patients.

The MDD patients who do not respond to an adequate dose and duration of antidepressant treatment are indicated for combined therapy. Many studies show that psychotherapy combined with antidepressants is effective for these patients. In the STAR*D study, the MDD patients who had received inadequate benefits from a initial antidepressant medication were assigned to treat with other strategies. The findings showed that CBT augmentation to citalopram is as effective as pharmacologic augmentation, although, the latter augmentation had more rapid remission than the CBT augmentation (Thase et al., 2007). Regarding the evidence from other ethnic groups, an open study also demonstrated the adding CBT to fluoxetine in Thai patients with MDD who did not respond to four weeks treatment of fluoxetine has significantly more efficacy than previous fluoxetine treatment alone (Maneeton et al., 2010).

4. Long-term treatment (continuation and maintenance phase)

After the successful treatment of MDD in the acute phase, the discontinuation of antidepressant therapy usually leads to a relapse or recurrent. Long-term treatment is, therefore, desperately needed for most patients. The ultimate goal of treatment phase is to sustain the remission period and prevent a new episode of MDD.

4.1 Antidepressants

Many reviews supported the antidepressant continuation for the prevention of early relapse for a period of 9-12 months after remission. Maintenance therapy of antidepressants is effective for preventing the recurrence of depressive episodes (Paykel, 2001). A systemic review of 31 studies including 4,410 participants demonstrated that antidepressant continuation treatment could reduce the relapse rate as comparison with placebo (41% for placebo vs. 18% for antidepressants) (Geddes, et al., 2003). Another meta-analysis of four comparative and 23 placebo-controlled trials reviewed the efficacy and effectiveness of second-generation antidepressants for preventing MDD relapse and recurrence during continuation and maintenance phases of treatment. Duloxetine and paroxetine, fluoxetine and sertraline, fluvoxamine and sertraline, and trazodone and venlafaxine were comparable for the relapse prevention of a depressive episode. A meta-analysis of those second-generation antidepressants indicated the overall benefits of continuation- and maintenance-phase treatment for patients with MDD (Hansen et al., 2008). In addition, a meta-analysis of 30 studies involving 4,890 participants also summarized that antidepressants could reduce a relapse risk in the maintenance phase, regardless of clinical and pharmacologic factors. However, the larger number of depressive episodes may suggest a relative resistance against the prophylactic treatment from antidepressant (Kaymaz et al., 2008).

A meta-analysis of Kok et al. (2011) reviewed eight studies of continuation and maintenance treatment in the elderly with 925 participating patients. The results showed that continuing treatment with antidepressants appeared to be efficacious as compared with placebo. The efficacy and tolerability during long-term treatment of both TCAs and SSRIs are comparable.

From those reviews, antidepressants appear to be effective in prevention relapse and recurrence of a depressive episode in MDD patients. However, the prophylactic effects of antidepressants in patients with many depressive episodes may not be as effective as those with a single episode.

4.2 Cognitive behavioral therapy

The review of Paykel (2001) showed that CBT appeared to be effective in preventing relapse from unipolar depression, particularly in patients with residual symptoms. A systemic review of 28 trials involving 1,880 adult patients suggested that acute treatment of CBT might be more effective than pharmacotherapy in reducing a relapse or recurrence of depressive episode. To compare with other active continuation treatments, continuation treatment with CBT in those responding to acute antidepressant therapy can reduce the relapse and recurrence at the end of continuation treatment and follow-up (Vittengl et al., 2007).

Several evidences also show the advantage of long-term treatment with CBT for depression. The clinical study of Fava et al. (1996) determined whether CBT of residual symptoms of depression can prevent further relapses. Forty MDD patients with successfully antidepressant therapy were randomly assigned to either CBT or standard clinical management. Antidepressant medications in both groups were gradually tapered. The result showed that CBT was effective for the reduction of relapse in the depressed patients.

As an intervention during the continuation and maintenance phase, CBT is beneficial for prevention of depressive episodes.

4.3 Cognitive-behavioural therapy combined with antidepressants

There is some evidence on the long-term benefits of psychotherapy combined with antidepressants. This combined therapy is particular effective in preventing a relapse of depressive episode. Although short-term antidepressant treatment is effective for MDD patients, some of them still behave and believe as if they depressed, and some still have low self-esteem or interpersonal difficulties. These residual symptoms, therefore, may be addressed with CBT. A 6-month, randomized controlled trial (RCT) compared the efficacy of continuation treatment with fluoxetine plus CBT or fluoxetine alone in 56 patients (ages 11-18 years) with MDD who have responded to acute pharmacotherapy. The findings indicated that fluoxetine plus CBT might be able to reduce the risk of relapse as compared with fluoxetine alone (Kennard et al., 2008). In an open trial, 19 patients who failed to respond to at least two trials of antidepressants with adequate doses and durations were treated with CBT augmentation. The remaining 16 patients improved significantly, and 12 patients were considered to be in remission (Fava et al., 1997).

In contrast, there is a 6-month, continuation treatment study in patients with MDD who were remitted from an 8-week, open-label, fixed dose, acute treatment of fluoxetine. The study compared the continuation treatment of fluoxetine only and fluoxetine plus CBT. The findings showed no significant differences in the respects of relapse rates and 17 HAM-D scores (Petersen et al., 2004).

5. Further research

Several lines of evidence suggest that antidepressants, CBT and their combination are effective for the treatment and prevention of depressive episodes. Most studies involved the

treatment in acute phase and the rests were in the continuation and maintenance phases. Although several reviews and clinical studies in acute phase treatment of MDD have been done, most of them involve only either antidepressant or CBT monotherapy. In addition, only few clinical studies and systematic reviews of MDD treatments in continuation and maintenance phases, particularly the cognitive-behavioural therapy combined with antidepressants, have been carried out. Further RCTs and systemic reviews with well-designed methodology, large sample sizes and consistent outcomes may be helpful in clarifying the benefits of this combination therapy in both acute and long-term treatments of MDD.

6. Conclusion

In the acute phase of MDD, combination of CBT and antidepressants appears to be more efficacious than antidepressant or CBT monotherapy, particularly in severely depressed patients. However this is a lack of evidence of this combination in depressed children and adolescents.

For long-term treatment of MDD, antidepressant medications, CBT and its combination appear to be effective in preventing a depressive episode in both continuation and maintenance phase. Since there were only limited studies of this, we could not conclude that this combination is superior to antidepressant or CBT monotherapy in these phases. More well-designed studies are, therefore, necessary to determine the superiority of this combination over antidepressant and CBT monotherapy.

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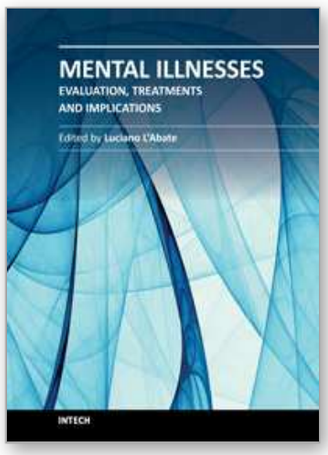
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In the book "Mental Illnesses - Evaluation, Treatments and Implications" attention is focused on background factors underlying mental illness. It is crucial that mental illness be evaluated thoroughly if we want to understand its nature, predict its long-term outcome, and treat it with specific rather than generic treatment, such as pharmacotherapy for instance. Additionally, community-wide and cognitive-behavioral approaches need to be combined to decrease the severity of symptoms of mental illness. Unfortunately, those who should profit the most by combination of treatments, often times refuse treatment or show poor adherence to treatment maintenance. Most importantly, what are the implications of the above for the mental health community? Mental illness cannot be treated with one single form of treatment. Combined individual, community, and socially-oriented treatments, including recent distance-writing technologies will hopefully allow a more integrated approach to decrease mental illness world-wide.

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