

rates, assessed by the 17-item Hamilton Rating Scale for Depression (HRSD-17) scores, were 17.6%, 24.8% and 21.3%, respectively (Figure 2).<sup>25</sup> Thus, approximately one in four depressed patients who did not tolerate or remit with citalopram achieved remission of symptoms after switching therapy to sustained-release bupropion, sertraline or venlafaxine.<sup>25</sup>

In the other group, patients who did not tolerate or achieve remission despite 11.9 weeks of citalopram therapy were randomized to receive augmentation treatment for 12 weeks with buspirone or sustained-release bupropion.<sup>26</sup> Buspirone is a partial agonist at the post-synaptic 5-hydroxy-tryptamine (5-HT) receptor, which enhances the activity of SSRIs through the 5-HT receptors. It is not viewed as an antidepressant monotherapeutic agent, whereas sustained-release bupropion is. At the end of the study, the sustained-release bupropion group and buspirone group had similar rates of the HRSD-17 remission (29.7% and 30.1%, respectively) and 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR-16) remission (39% and 32.9%, respectively). These rates were relatively greater than those in patients in Level 2 of the STAR\*D trial who switched therapy (Figure 2).<sup>25,26</sup> According to Professor Papakostas, this might serve as preliminary evidence to suggest that augmentation might be better than switching treatment in patients who do not achieve remission with first-line SSRI treatment.

Professor Papakostas pointed out that when patients with partial response to a first-line agent are switched to another medication, they risk losing the benefits acquired from the first-line drug and not gaining those back from the second-line agent. Furthermore, patients who discontinue SSRIs and SNRIs may suffer from troublesome withdrawal symptoms such as agitation, profound anxiety, irritability, insomnia, nausea, nightmares, etc. This increases the risk of worsening of clinical picture in patients who switch, a phenomenon not observed in patients who receive treatment augmentation. Thus, he prefers augmenting therapy to switching therapy for patients with partial response.

### Conclusions

Residual symptoms of sleepiness and fatigue are widely prevalent among MDD remitters and are resistant to treatment. Thus, physicians must focus on resolving these in addition to the symptoms of depression in all MDD patients. Bupropion appears to be more effective than SSRIs in treating residual symptoms in MDD. Bupropion is also appropriate for second-line therapy in MDD patients not responding to primary treatment.

### References

- Papakostas GI, Fava M. *Eur Neuropsychopharmacol* 2009;19:34-40.
- Nierenberg AA, et al. *J Clin Psychiatry* 1999;60:221-225.
- Fava M, et al. *J Clin Psychiatry* 2006;67:1754-1759.
- Baldwin DS, Papakostas GI. *J Clin Psychiatry* 2006;67(Suppl 6):9-15.
- Paykel ES, et al. *Psychol Med* 1995;25:1171-1180.
- Simon GE, et al. *Gen Hosp Psychiatry* 2000;22:153-162.
- Papakostas GI, et al. *J Clin Psychopharmacol* 2004;24:507-511.
- Posternak MA, Zimmerman M. *Arch Gen Psychiatry* 2002;59:70-76.
- Horwath E, et al. *J Affect Disord* 1992;26:117-125.
- Tylee A, et al. *Int Clin Psychopharmacol* 1999;14:153-165.
- Tylee A, et al. *Int Clin Psychopharmacol* 1999;14:139-151.
- Fava GA, et al. *J Affect Disord* 1990;19:149-152.
- Addington AM, et al. *Psychol Med* 2001;31:1037-1044.
- Ford DE, Cooper-Patrick L. *Depress Anxiety* 2001;14:3-6.
- Roberts RE, et al. *Am J Psychiatry* 2000;157:81-88.
- Judge R, et al. *J Clin Psychopharmacol* 2000;20:666-672.
- Papakostas GI. *Eur Neuropsychopharmacol* 2006;16:391-402.
- Jefferson JW, et al. *J Clin Psychiatry* 2006;67:865-873.
- Stahl SM, et al. *J Clin Psychiatry* 2003;64(Suppl 14):6-17.
- Brody AL, et al. *Biol Psychiatry* 2001;50:171-178.
- Quitkin FM, et al. *Arch Gen Psychiatry* 1990;47:935-941.
- Papakostas GI, et al. *Biol Psychiatry* 2006;60:1350-1355.
- Papakostas GI, et al. *J Psychiatr Res* 2006;40:370-373.
- Fava M, et al. *Ann Clin Psychiatry* 2007;19:153-159.
- Rush AJ, et al. *N Engl J Med* 2006;354:1231-1242.
- Trivedi MH, et al. *N Engl J Med* 2006;354:1243-1252.

## HKCPMA Certificate Course

### Management of Common Mood Disorder in the Primary Care Setting

Date: 27 April-6 July 2010

Time: 1:00-3:30 pm (lecture & lunch)

Venue: Eaton Hotel Hong Kong

Lecture	Date	Topic
1	27 April (Tues)	Overview of Anxiety Disorders: Etiology, Symptoms, Diagnosis
2	11 May (Tues)	Designing a Comprehensive Treatment Plan for Anxiety Disorder in Primary Care
3	25 May (Tues)	Tackling Bipolar Disorder in Primary Care
4	8 June (Tues)	Tips for Managing MDD in Your Everyday Practice
5	22 June (Tues)	How to Pick Out Those Patients with Mood Disorders?
6	6 July (Tues)	Communication Skills: History Taking and Counseling

#### Registration Fee

HKD\$300 for the whole course (6 lectures)

HKD\$100 for single lecture

For registration enquiry and enrolment form

Please contact **Ms Mabel Chow**: Mabel.m.chow@gsk.com



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## HKCPMA Newsletter

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**Contact us:**  
The Hong Kong Community Psychological Medicine Association (HKCPMA) Limited  
G/F, Shop 6, Tsz Ping House  
Tin Tsz Estate, Yuen Long, NT  
Telephone: 2617 9939  
Fax: 2446 6773  
Website: <http://www.hkcpma.com>  
Email: [admin@hkcpma.com](mailto:admin@hkcpma.com)

**Chairman:**  
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### Message from the Chairman



This is the second term I am serving as Chairman of the Hong Kong Community Psychological Medicine Association (HKCPMA), and I always view it as a privilege to write a short message to fellow members in the Newsletter. The new council was elected on 29 October 2009. We would like to express our gratitude to Dr Mark Chan who has retired as our Secretary and is now replaced by Dr Charles Yan, and a warm welcome to Dr Samuel Chan as he joins our workforce.

The activities of the HKCPMA will continue throughout this summer, with the HKCPMA Certificate Course: "Management of Common Mood Disorder in the Primary Care Setting", sponsored by Glaxo-SmithKline, spreading out from April to July.

There is a growing population uncovered with mental problems. It is sad but true that mild symptoms do progress to debilitating illnesses without early diagnosis and proper treatment and, ultimately, result in tragedies. The importance of screening patients with mood disorders in daily practice is hence no secret to anyone, and the HKCPMA is keen to take steps to promote early detection of mental symptoms of patients.

Through experience sharing and interactive case demonstrations, the upcoming six lectures aim to update general practitioners with practical psychiatry knowledge. By the end of the course, we hope that you will have acquired crucial skills to recognize and handle basic psychiatric problems.

We are looking forward to seeing those of you who have enrolled in this certificate course. Your dedication and commitment is the bedrock to the success of the course.

Dr Aaron Lee Fook Kay  
Chairman, HKCPMA

# Role of norepinephrine and dopamine in the management of residual symptoms in major depressive disorder

Patients with major depressive disorder (MDD) who remit with standard antidepressant therapy often continue to experience residual symptoms of depression, including sleepiness and fatigue, which are often difficult to treat. The ultimate goals of therapy in MDD should include relieving symptoms of depression which are significant enough to result in discomfort, distress and functional impairment, including residual symptoms. During a recent dinner symposium, Professor Papakostas outlined the role of norepinephrine and dopamine in the treatment of residual symptoms in MDD and suggested treatment strategies for their management. He also presented evidence involving the use of bupropion (Wellbutrin®, GSK), a norepinephrine-dopamine reuptake inhibitor (NDRI) antidepressant, to achieve clinical remission and reduce residual symptoms in MDD patients.



**George I Papakostas, MD**  
 Director, Treatment-Resistant Depression Studies  
 Massachusetts General Hospital  
 Associate Professor of Psychiatry  
 Harvard Medical School  
 Boston, USA

who achieve remission with standard antidepressant therapy. These symptoms include hypersomnia or sleepiness, fatigue, diminished interest or pleasure, guilt and poor concentration.<sup>2,3</sup> It has been observed that when fluoxetine, a selective serotonin reuptake inhibitor (SSRI), was used for treating depressed patients with pre-existing complaints of excessive sleepiness and fatigue, there was a high likelihood of persistence of these complaints even after remission.<sup>4</sup>

## Importance of treating residual symptoms in MDD patients

MDD treatment should be aimed at relieving symptoms of depression as well as residual symptoms. Patients in remission with residual symptoms have higher relapse rates and greater psychosocial and work impairment than those without residual symptoms.<sup>5-7</sup> There is a wide prevalence of symptoms of lethargy and fatigue among depressed patients.<sup>8,9</sup> In a survey of 1,884 European patients who consulted a physician about depression, 73% of patients reported feeling tired, having no energy and/or being listless during their MDD episode. Their symptoms were predominated by complaints of low mood, fatigue, sleep problems and anxiety.<sup>10,11</sup> Professor Papakostas emphasized that it is advisable to manage such symptoms early in the disease as these are difficult to treat when they present as residual symptoms after antidepressant therapy.

Moreover, studies have shown that people who complain of unexplained fatigue and excessive sleepiness have an increased risk for MDD than those who do not have these complaints, suggesting that lethargy may have a physiological association with MDD.<sup>12-15</sup>

## Strategies for treating residual symptoms in MDD patients

### 1. Selecting agents which are less likely to exacerbate residual symptoms

When treating depression, it is advisable to avoid medications with anticholinergic and antihistaminic actions which are known to induce fatigue and sleepiness, such as tricyclic antidepressants (TCAs), trazodone and mirtazapine. It is preferable to use less sedating agents, such as NDRI, SSRIs, norepinephrine reuptake

inhibitors (NRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs).<sup>4</sup>

### 2. Selecting agents that are effective in treating sleepiness and fatigue

Studies have shown that both fluoxetine and bupropion are effective in treating symptoms of depression, including fatigue.

Data from pooled analysis of 7 clinical trials involving 2,075 MDD patients showed that overall depression was significantly better controlled in fluoxetine-treated patients than placebo-treated patients ( $p < 0.001$ ).<sup>16</sup> Also, fluoxetine was significantly more effective than placebo in improving fatigue in MDD patients ( $p < 0.001$ ).<sup>16</sup>

## “MDD treatment should be aimed at relieving symptoms of depression as well as residual symptoms”

Bupropion has been shown to be as effective as SSRIs, and more effective than placebo in terms of eliciting remission in MDD patients.<sup>17</sup> In one study, treatment of MDD patients with extended-release bupropion was superior to placebo in improving depression measured by the 30-item Inventory of Depressive Symptomatology-Self Report (IDS-IVR-30) total score ( $p = 0.018$ ), as well as improving symptoms of decreased energy, pleasure, and interest in these patients ( $p = 0.007$ ).<sup>18</sup>

Given that catecholamines (norepinephrine and dopamine) are linked with vigilance, energy, wakefulness and attention, Professor Papakostas remarked that it may be hypothesized that drugs with catecholaminergic actions have better efficacy than those without catecholaminergic actions for treating residual symptoms of fatigue and sleepiness in MDD.<sup>19,20</sup> For instance, an older study demonstrated that in patients with atypical depression, a condition characterized by symptoms of mood reactivity along with hypersomnia, fatigue, increased appetite, etc, treatment with phenelzine, a drug with dopaminergic effects, had better efficacy than imipramine, which does not have dopaminergic effects ( $p < 0.05$ ).<sup>21</sup>

Professor Papakostas and colleagues pooled data from 6 placebo-controlled studies that compared the efficacy of bupropion with placebo and SSRIs such as sertraline, paroxetine and escitalopram, in treating sleepiness and fatigue in MDD patients. They noticed significantly greater improvement in hypersomnia scores among bupropion-treated than SSRI-treated ( $p < 0.0001$ ) or placebo-treated patients ( $p = 0.0008$ ). There was also significantly greater improvement in fatigue scores among bupropion-treated ( $p < 0.0001$ ) and SSRI-treated ( $p = 0.0005$ ) than placebo-treated patients, and among bupropion-treated than SSRI-treated patients ( $p = 0.0078$ ).<sup>22</sup> In addition, compared with SSRI-remitters, fewer bupropion-remitters experienced residual symptoms of hypersomnia ( $p = 0.0014$ ) and fatigue ( $p = 0.0020$ , Figure 1).<sup>22</sup> Thus, bupropion is an effective agent for treating depression and residual symptoms of sleepiness and fatigue, and is more effective than SSRIs for managing these residual symptoms.

### 3. Treatment augmentation to relieve residual fatigue and sleepiness

MDD treatment often requires addition of a second agent to

augment the first, although the efficacy of this strategy has not been studied in many randomized controlled trials.

A small study was conducted among MDD patients in remission or partial response who complained of residual symptoms of fatigue. Augmentation of existing treatment with atomoxetine for at least 4 weeks resulted in significant improvement in fatigue scores in these patients ( $p < 0.0466$ ).<sup>23</sup>

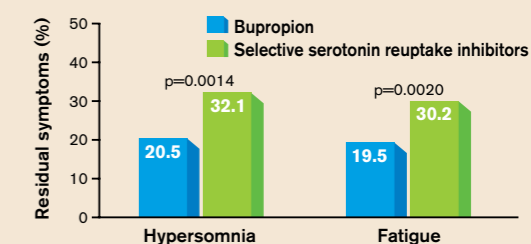
Another study examined the benefits of modafinil augmentation for 6–8 weeks in patients who were partial responders to treatment with SSRI and complained of residual symptoms of sleepiness and fatigue. Compared with placebo, modafinil augmentation rapidly (within 1 week) and significantly improved overall clinical condition and symptoms of fatigue, wakefulness and depression ( $p < 0.01$  for all).<sup>24</sup>

The STAR\*D (Sequenced Treatment Alternatives to Relieve Depression) team conducted large, multicentre, randomized, controlled trials to assess the effectiveness of depression treatments in MDD patients. The common first-step treatment for MDD patients is SSRI. In the STAR\*D trial, patients who failed to tolerate or remit with initial treatment with citalopram (Level 1) progressed to Level 2 of the trial:

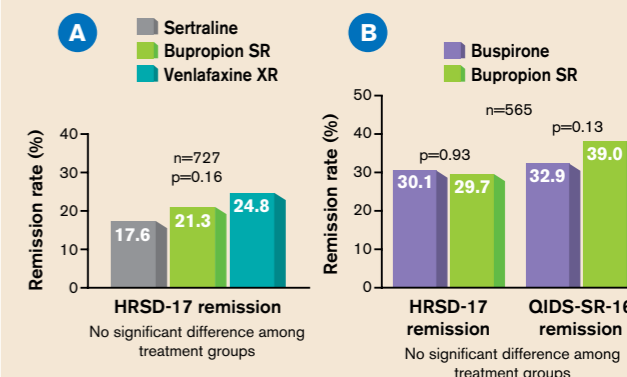
1. Switching treatment to sertraline, venlafaxine or sustained-release bupropion<sup>25</sup>, or
2. Treatment augmentation with buspirone or sustained-release bupropion.<sup>26</sup>

Among patients who switched treatment to sertraline, venlafaxine or sustained-release bupropion for up to 14 weeks, remission

**Figure 1. Residual symptoms in major depressive disorder remitters<sup>22</sup>**



**Figure 2. STAR\*D trial – Primary efficacy outcomes with switching (A) and augmenting (B) treatment<sup>25,26</sup>**



Bupropion SR=sustained-release bupropion; Venlafaxine XR=extended-release venlafaxine; HRSD-17=17-item Hamilton Rating Scale for Depression; QIDS-SR-16=16-item Quick Inventory of Depressive Symptomatology-Self-Report score; STAR\*D=Sequenced Treatment Alternatives to Relieve Depression