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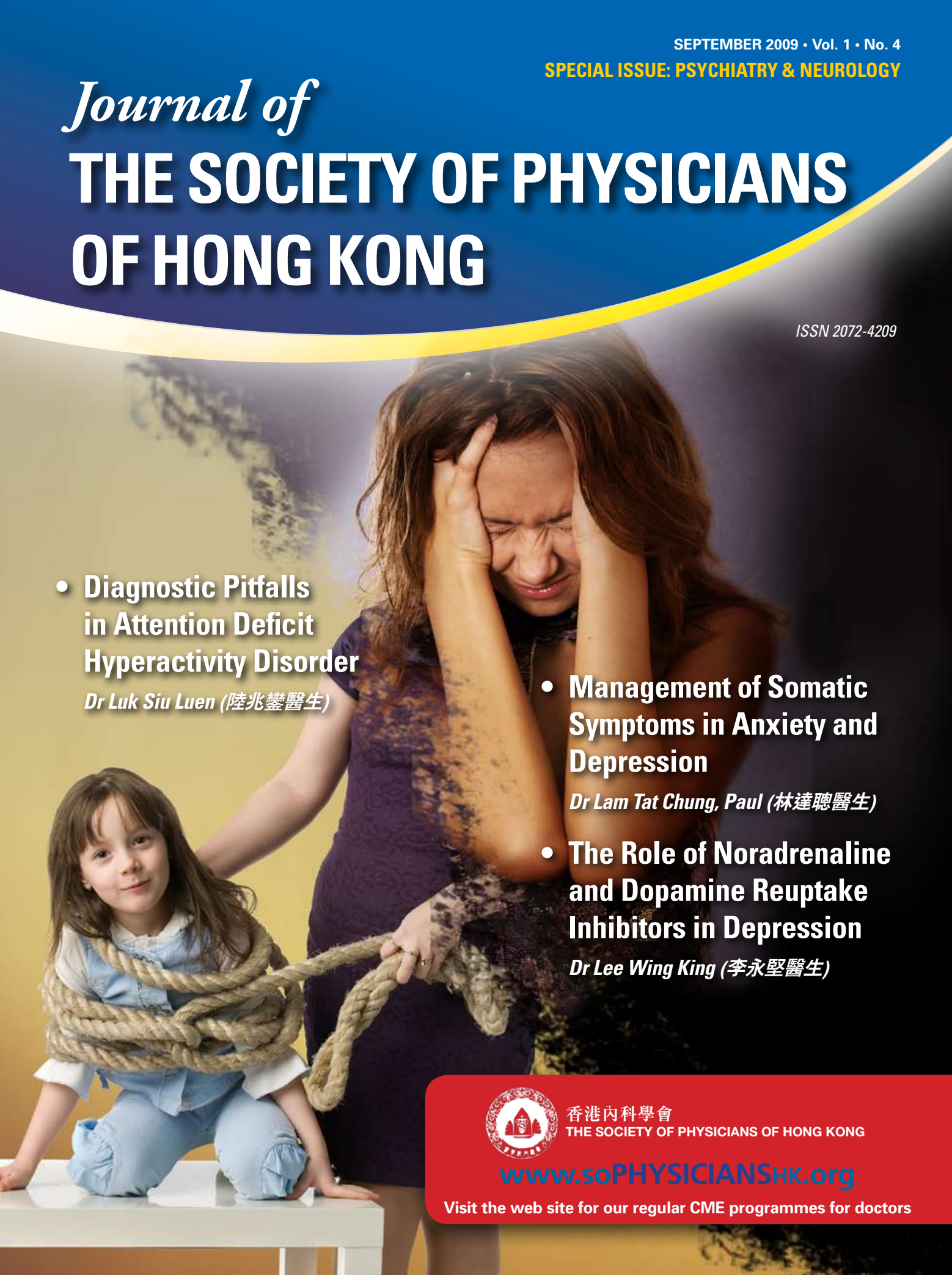

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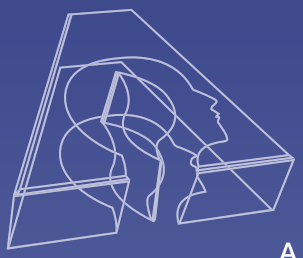

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Editorial

Until recent years, Psychiatry was a rather remote subject to the average doctor, who was puzzled and alarmed by illness concepts and treatment methods which were quite different from what they were taught or accustomed to. Doctors faced such patient with awe, uncertainty and total lack of confidence. Their usual reaction was to get the patient out of their hands as soon as possible.

With a significantly improved curriculum in Psychiatry in medical schools, together with heightened awareness among practicing doctors and availability of continuing medical education programmes in Psychiatry, the situation has changed tremendously. Postgraduate programmes in Psychiatry are now some of the most popular educational events participated by medical practitioners. In addition, with the development of effective treatment methods, doctors nowadays are much more confident and capable of dealing with psychiatric conditions. We hope this issue of the Journal in Psychiatry will benefit all practitioners who have to deal with psychiatric aspects of their patients.

Dr Lam Tat Chung, Paul
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** Adapted from Simon et al. A double blind, placebo controlled clinical study evaluating the efficacy of extended release venlafaxine in the prevention of relapse of depression. Cumulative relapse rates at 3 and 6 months were 19 and 28% respectively for venlafaxine XR and 44 and 52%, respectively for placebo.[2]

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Management of Somatic Symptoms in Anxiety and Depression

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Key words:
Anxiety (焦慮症), depression (抑鬱症), somatic symptoms (軀體症狀), pain (痛楚), serotonin norepinephrine reuptake inhibitors (血清素及正腎上腺素再吸收抑制劑)

Case Study

A 55-year-old female suffered from severe pain in her lower back and sciatica-like pain in her right lower limb. The pain was agonizing and disabling, so that she had to lie in bed all day.

She also complained of precordial gripping pain, agitation, weepiness, depressive mood and insomnia. She came from a family with a history of depressive illness, and suicide in many blood relations. A daughter, to whom the patient was attached emotionally, died recently. Multiple investigations including MRI scans revealed no abnormality. The patient was thoroughly checked by orthopaedic surgeons who declared that no physical cause could be found. Psychological exploration revealed that the patient's father, who died some years ago, also suffered from severe pain in the lower limb in his terminal illness, and was nursed by the patient. The patient was treated as a case of depressive illness with psychogenic pain. She obtained significant relief from treatment with venlafaxine XR.

Somatic Symptoms: Signs of Underlying Mood and Anxiety Disorders

Doctors often encounter in their clinics patients presenting with unexplained somatic symptoms. Such symptoms may constitute more than 30% of the physical complaints from patients.[1] Some of these complaints may be relatively short-lived and mild, but others are prolonged, agonizing and disabling, resulting in frequent consultations, repeated investigations and imposing a great burden on medical resources.

Studies have shown that a high percentage of patients with somatic symptoms suffer from an underlying anxiety or depressive disorder. Kroenke showed that the reporting of any physical symptom by patients increased the likelihood of a mood or anxiety disorder by two to three times, and the rate of anxiety and depressive disorder was related to the number of symptoms reported.[2] (Table 1)

Table 1. Number of patient-reported physical symptoms and rate of anxiety and depressive disorder

Number of somatic symptoms	0–1	2–3	4–5	6–8	≥9
Rate of anxiety and depressive disorder	2%	12%	23%	44%	60%

Adapted from reference 2.

Psychiatric Disorders Often Missed in Patients With Somatic Complaints

Patients with mood or anxiety disorder often present to their doctors with physical symptoms. Over two-thirds of depressed patients presented exclusively with somatic complaints,[3] often from multiple areas of the body. Half of the depressed patients had unexplained physical symptoms and 11% denied any symptoms of depression. In addition, 70% to 80% of patients with depression

also manifested somatic symptoms.[4]

In patients with a preponderance of physical symptoms, affective and anxiety disorders are often missed. Such physical complaints may include pain, dizziness, weakness or insomnia, etc. It is simple and convenient for the primary care doctor to prescribe an analgesic or a hypnotic, but without management of the underlying psychiatric condition, the patient will return soon and frequently, often with increased severity and disability. One study showed that if depressed patients presented to their doctors with a medical disorder, the chance of detection of the underlying affective disorder was 20%.[5] If they presented with somatic symptoms, the chance was 50%.[5] Many other studies showed much lower detection rates. Therefore, doctors are well advised to look out for underlying anxiety and affective disorders in patients with somatic symptoms, especially multiple unexplained ones.

Treatment of Anxiety or Mood Disorder Reduces Somatic Symptoms

Management of this group of patients should aim at earlier detection, earlier intervention and effective therapy to achieve remission of the mood or anxiety disorder. Doctors should be vigilant of an underlying anxiety or mood disorder in their patients especially if they are from a high-risk group. This includes those with chronic medical illnesses, recent psychological stress, past and family history of mood disorder, pregnant and postpartum women, and patients with substance or alcohol abuse, etc.

Treatment of the underlying anxiety or mood disorder was shown to be efficacious in reducing somatic symptoms. In one study, Kroenke treated more than 600 patients with depression for 9 months with selective serotonin reuptake inhibitors (SSRIs) and followed their somatic symptoms with the Patient Health Questionnaire (PHQ-15) Somatic Symptom Module.[6] Within the first month of antidepressant treatment, a substantial proportion of depressed patients reported improvement of their physical symptoms.[6] Pain symptoms were found to be least responsive to SSRI treatment.[6] In another study, Bradley investigated the effect of venlafaxine XR on 197 depressed patients who were unresponsive to tricyclic antidepressants or SSRIs, and used the Visual Analogue Scale (VAS) to track the severity of pain.[7] The VAS score for pain decreased from 8.4 to 3.6 after 1 year of treatment ($p<0.001$), and the quality of life score improved significantly.[7]

"Look out for underlying anxiety and affective disorders in patients with somatic symptoms, especially multiple unexplained ones"

Vanlafaxine: Drug of Choice for Treating Somatic Symptoms

Recent studies have revealed that depression and pain share common neurochemical and neuroanatomic pathways. Serotonin and norepinephrine are two neurotransmitters involved, and they control a pain modulating circuit in the central nervous system.[8,9] Fishbain analyzed data from human and animal studies and found that dual serotonergic and noradrenergic reuptake inhibitors are more effective than either noradrenergic or serotonergic reuptake inhibitors alone in the treatment of various models of acute, chronic and neuropathic pain.[10] In another study, he demonstrated the superiority of dual-acting agents in the treatment of headache, fibromyalgia and diabetic neuropathy compared with SSRI treatment.[11] In a review paper, Sussman also concluded that dual-acting antidepressants are more effective in treating both the painful physical symptoms and mood symptoms of depression.[12]

The somatic symptoms of generalized anxiety disorder (GAD) are likewise relieved by treatment with the dual-acting agent, venlafaxine XR. A post-hoc analysis by Stahl of pooled data from five placebo-controlled, double-blind randomized studies in patients with GAD revealed that somatic muscular, cardiovascular and respiratory symptoms improved significantly by week 1, as with psychiatric symptoms; all other somatic symptoms improved by week 2.[13] Additional improvement was seen with continuing treatment for up to 6 months.

Conclusions

Unexplained somatic symptoms are frequently encountered in medical practice. Underlying anxiety and depression are frequently present in such patients, but the diagnosis is often missed. Treating the psychiatric disorder often results in relief of the somatic symptoms.

Pain and depression share common neurochemical and neuroanatomic pathways. Dual reuptake inhibitors, particularly venlafaxine, are effective in relieving such somatic symptoms. Studies showed that they are superior to agents acting on either serotonin or norepinephrine alone.

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*Bupropion is approved for use in over 50 countries for the treatment of major depressive disorder and / or as an aid to smoking cessation under the brand name of Zyban™ (data on file, GlaxoSmithKline Research Triangle Park, N.C.)

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Treatment of patients with renal impairment should be initiated at reduced dosage. Patients with hepatic or renal impairment should be closely monitored for possible adverse effects (e.g., insomnia, dry mouth, seizures) that could indicate high drug or metabolite levels. Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents <18 years with major depressive disorder and other psychiatric disorders. Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Neuropsychiatric symptoms have been reported. In particular, psychotic and manic symptomatology has been observed, mainly in patients with a known history of psychiatric illness. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. There is limited clinical experience of the use of bupropion to treat depression in patients with cardiovascular disease. Care should be exercised if it is used in these patients. **INTERACTIONS** Care should be exercised when bupropion is co-administered with drugs known to affect the CYP2B6 isoenzyme Concomitant therapy with drugs predominantly metabolised by this isoenzyme should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a medication metabolised by CYP2D6, the need to decrease the dose of the original medication should be considered. Rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during bupropion treatment. Administration of bupropion to patients receiving either levodopa or amantadine concurrently should be undertaken with caution. Studies suggest that exposure to bupropion may be increased when sustained release bupropion tablets are taken with food. Concomitant use of bupropion and a Nicotine Transdermal System (NTS) may result in elevations of blood pressure. Interactions have been reported with citalopram and ritonavir. Exercise caution before driving or use of machinery until they are reasonably certain bupropion does not adversely affect their performance. **PREGNANCY AND LACTATION** Administration of bupropion should only be considered during pregnancy if the expected benefits are greater than the potential risks. As bupropion and its metabolites are excreted in human breast milk, mothers should be advised not to breast feed while taking immediate release, sustained release or extended release bupropion tablets. **ADVERSE REACTIONS** Hypersensitivity reactions such as urticaria, Anorexia. Weight loss, Insomnia, Agitation, anxiety, Depression, confusion. Headache, Tremor, dizziness, taste disorders, Concentration disturbance, Seizures, Visual disturbance. Tinnitus. Tachycardia. Increased blood pressure (sometimes severe), flushing. Dry mouth, gastrointestinal disturbance including nausea and vomiting. Abdominal pain, constipation. Rash, pruritus, sweating. Fever, chest pain, asthenia. **OVERDOSAGE** In addition to those events reported under Adverse Reactions, overdose has resulted in symptoms including drowsiness, loss of consciousness and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias. In the event of overdose, hospitalisation is advised. 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The Role of Noradrenaline and Dopamine Reuptake Inhibitors in Depression

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MBChB (HK), MRC Psych (UK), FHKC Psych, FHKAM (Psych)

Specialist in Psychiatry

Key words:
Depression (抑鬱症), norepinephrine and dopamine reuptake inhibitors (去甲腎上腺素/多巴胺苯丙胺循環抑制劑), bupropion (苯丙胺)

Introduction

Depression is a common mental disorder. The World Health Organization (WHO) identified depression as the fourth leading contributor to the global burden of disease in terms of disability-adjusted life years (DALYs) in 1990 and estimated that it will take the second place of DALYs for all ages by 2020.[1-3] Major depressive disorder (MDD) is usually characterized by depressed mood, loss of interest and/or loss of energy.[4] A large-scale community survey on mental health in Hong Kong showed that mood disorder is one of the commonest conditions especially among female subjects.[5] The prevalence of mental disorders in primary care is very high, reaching up to 60% in different recent studies.[6-8]

MDD is a neurochemical disorder arising from hypofunctioning of monoamine systems.[9] Neurotransmitters in the synaptic cleft between neurons such as serotonin, norepinephrine (NE) and dopamine (DA) are monoamines believed to be associated with different symptoms.[4]

Treatments

Treatments for depression include medication, psychotherapy and electroconvulsive therapy. Classical antidepressant medications are tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs). There are several medications with a dual effect, including norepinephrine and dopamine reuptake inhibitors (NDRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).[9-11] (Table 1)

SSRIs are commonly used antidepressants.[10] They increase the extracellular level of serotonin by inhibiting its reuptake into the presynaptic cell, thus increasing the level of serotonin available to bind to the postsynaptic receptor. Increased serotonin enhances neurotransmission.

NDRI Therapy

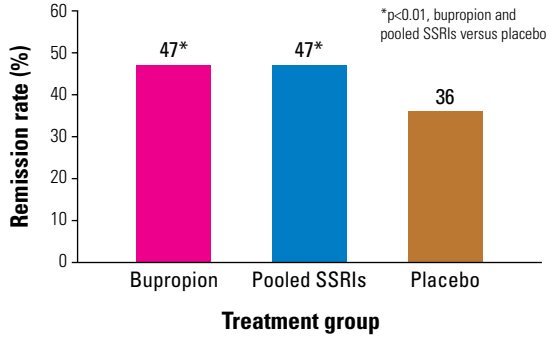
NDRIs enhance monoaminergic neurotransmission differently from other antidepressants. The mechanism of action involves dual reuptake inhibition of DA and NE. NDRIs do not alter serotonergic

Table 1. Various pharmacotherapies for major depressive disorder

Therapeutic class	Example	Monoaminergic effect	Mechanism of action
SSRI	Escitalopram	Serotonin reuptake inhibition	Blocking serotonin uptake at all serotonergic synapses
SNRI	Venlafaxine	Dual serotonin and norepinephrine reuptake inhibition	Potent inhibition of serotonin followed by norepinephrine uptake; no inhibition of monoamine oxidase activity; down-regulation of β-adrenergic receptors after chronic treatment
NDRI	Bupropion	Dual norepinephrine and dopamine reuptake inhibition	Potent inhibition of dopamine and norepinephrine uptake; no known influence on serotonin mechanism; free of anticholinergic and antihistaminergic activity

NDRI = norepinephrine and dopamine reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor
Adapted from references 9–11.

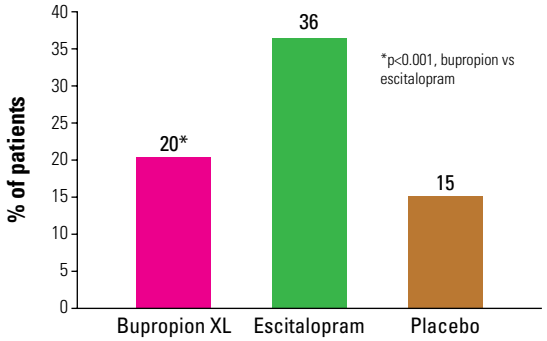
Figure 1. Remission rates at week 8 or endpoint for bupropion, SSRIs and placebo



Study design: Data of individual patients were pooled to compare the remission rates with NDRIs and SSRIs from a complete set of 7 randomized, double-blind studies comparing bupropion (n=732) with SSRIs (n=731) in outpatients with MDD; 4 studies included a placebo. Response and remission rates were compared at week 8 or endpoint.

MDD = major depressive disorder; NDRIs = norepinephrine and dopamine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors
Adapted from reference 12.

Figure 2. Percentage of patients at treatment week 8 with worsened sexual functioning



Study design: Adult outpatients with moderate to severe MDD and normal sexual functioning were randomly assigned to receive bupropion XL (n=276), escitalopram (n=281) or placebo (n=273) for up to 8 weeks. Data from 2 identically designed, randomized, double-blind, parallel-group studies were analyzed to compare the effects on sexual functioning.

MDD = major depressive disorder; XL = extended release
Adapted from reference 17.

neurotransmission either presynaptically or postsynaptically.[9]

Bupropion is the only NDRI antidepressant available in the market. A pooled analysis of all comparative trials of bupropion vs SSRIs demonstrated identical remission rates.[12] (Figure 1) Bupropion has no relevant affinity for histamine and/or serotonin receptors, and is not associated with side effects caused by SSRIs. In addition, bupropion is well tolerated with long-term use.[9]

Bupropion has been added to the treatment of patients with MDD who are partially or not responding to SSRIs. It has also been used alone in newly diagnosed patients.[13]

A large-scale study of MDD funded by the US National Institute of Mental Health, named Sequenced Treatment Alternatives to Relieve Depression (STAR*D), has been conducted to assess the effectiveness of treatments in generalizable clinical settings and ensure the delivery of adequate treatment. The results were published in 2006. In level 2 of the study, patients who were initially treated with citalopram, a SSRI, were either switched to or augmented with other antidepressants.[14] Those patients who fared better with the initial treatment and experienced minimal intolerance preferred augmentation, while those with little benefit from or substantial intolerance to the initial treatment preferred to switch.[15] Results suggested that switching either within (citalopram to sertraline) or out of class (citalopram to bupropion) was as effective as switching to the dual-action venlafaxine. Augmentation with bupropion showed no difference from that with buspirone.[15] However, bupropion was recommended due to its better tolerability, with fewer adverse events.[15,16]

The tolerability profile of bupropion differs from that of other antidrepressants.[9] Side effects which are often seen with SSRIs, such as sexual dysfunction, weight gain and somnolence, occur less frequently with bupropion and are comparable to placebo.[9,13] The most commonly reported adverse events of bupropion include headache, dry mouth, nausea, insomnia, constipation and dizziness.[13] These side effects have also been reported with other antidepressants.[9]

Sexual Dysfunction

Effects on sexual functioning are an important consideration in selecting antidepressant therapy because sexual dysfunction can affect a patient's quality of life.[17] Sexual dysfunction is frequently associated with SSRI treatment.[13] Bupropion is associated with a lower incidence of sexual dysfunction than SSRIs.[9,13] The agent was found to have a significantly more favourable profile on sexual function than escitalopram and venlafaxine.[17,18] (Figure 2)

Weight Gain

In addition to sexual dysfunction, weight gain may occur frequently with SSRIs, especially during long-term treatment, possibly via a serotonergic mechanism.[9] In contrast, bupropion was not shown to be associated with weight gain in various clinical trials.[9,13]

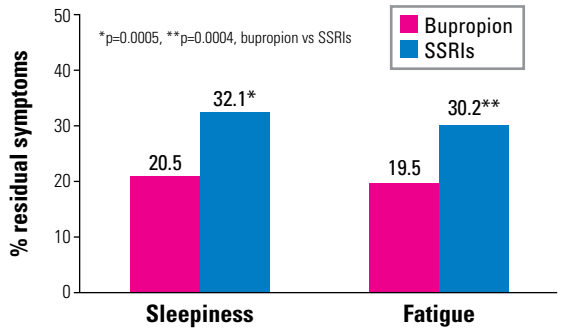
Sleepiness and Fatigue

Treatment of MDD with bupropion resulted in greater resolution of sleepiness and fatigue than SSRI treatment.[19] (Figure 3)

Anxiety

A clinically significant burden of comorbid anxiety symptoms in MDD is associated with greater severity and chronicity of illness, greater functional impairment, an increased risk of suicidality and a higher risk of depressive relapse.[20] Bupropion

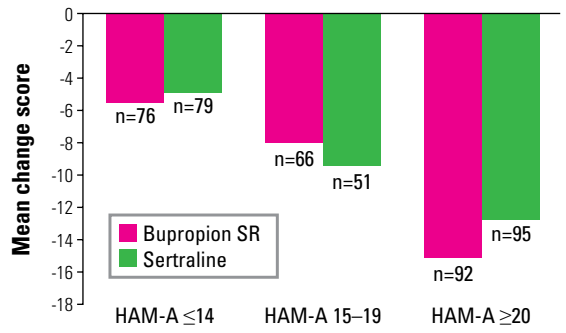
Figure 3. Sleepiness and fatigue in MDD remitters



Study design: Six double-blind, randomized clinical trials comparing bupropion (n=662) with an SSRI (n=655) for the resolution of sleepiness and fatigue in MDD patients were pooled. Hypersomnia and fatigue scores were evaluated.

MDD = major depressive disorder, SSRIs = selective serotonin reuptake inhibitors
Adapted from reference 19.

Figure 4. HAM-A mean change scores (LOCF) at day 56 for patients with different baseline scores



Study design: Analysis of pooled data from 2 identical, 8-week, acute phase, double-blind, placebo-controlled, parallel-group studies of bupropion (n=234), sertraline (n=225) and placebo (n=233) was conducted to examine the effects of bupropion and sertraline on anxiety in outpatients with recurrent MDD. Symptoms of anxiety and depression were evaluated.

HAM-A = Hamilton Rating Scale for Anxiety; LOCF = last observation carried forward; SR = sustained release
Adapted from reference 21.

is an appropriate option for patients with comorbid anxiety because it is efficacious in reducing symptoms of depression-related anxiety.[13] It has been shown to be as effective as SSRIs such as sertraline, with an equally rapid onset of anxiolytic activity.[21] (Figure 4)

Improving Energy, Pleasure and Interest

Other common MDD symptoms include fatigue, low energy and anhedonia, occurring in at least 70% of patients. Studies showed that symptoms of decreased energy, pleasure and interest were significantly improved, and insomnia was significantly reduced, in the bupropion group compared with placebo.[4]

"Bupropion is an appropriate option for patients with comorbid anxiety"

Conclusion

In Hong Kong, bupropion is prescribed for newly diagnosed depressive patients, as an augmentation to existing antidepressant treatment, or as a switch from other antidepressants when patients are suffering from side effects such as sexual dysfunction or do not respond to current treatment. The usual starting dose is 150 mg once daily. It is recommended that patients take bupropion in the morning to improve motivation for the rest of the day, and to avoid insomnia. In some situations, if necessary, it may be prescribed at a dosage of 150 mg twice daily. The usual side effects are nausea and dry mouth, with no complaints of serious side effects. Because of the good and distinct efficacy and tolerability profile, many patients who are either employed or still in school may prefer bupropion. In most cases, mood improvement can be observed after 3 to 4 weeks of treatment.

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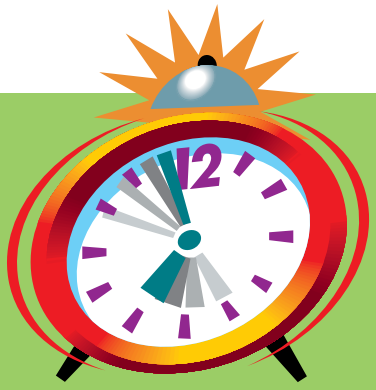
Attention Deficit Hyperactivity Disorder (ADHD)



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Diagnostic Pitfalls in Attention Deficit Hyperactivity Disorder

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Key words:
Attention deficit hyperactivity disorder (專注不足及過度活躍症), diagnosis (診斷)

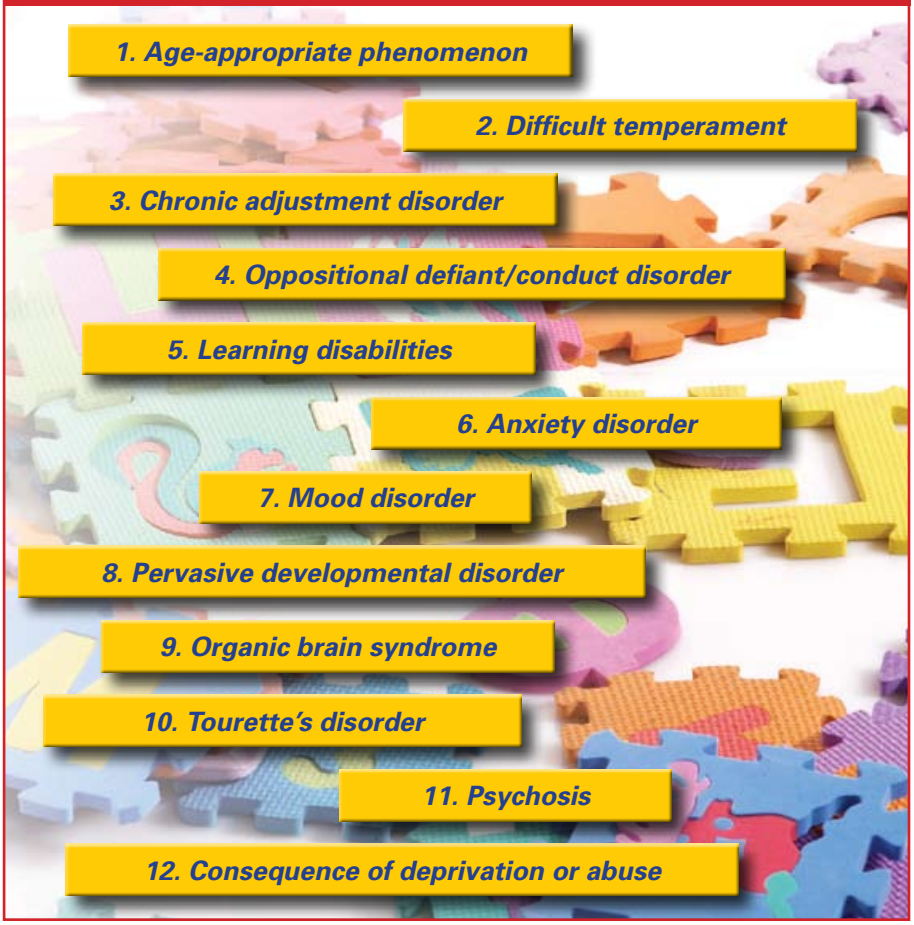
Attention deficit hyperactivity disorder (ADHD) is a common chronic and disabling condition in children. The focus of this paper is on diagnostic pitfalls. Two hypothetical clinical vignettes would illustrate the problem.

Vignette 1: A 6-year-old boy was brought to see a medical practitioner. The mother had read about ADHD from a magazine and felt that her son showed most of the symptoms described in the symptom checklist for ADHD. When seen at the clinic, the child was restless and was uncooperative when the doctor tried to engage him. The doctor then decided to prescribe medication as a trial of treatment.

Vignette 2 concerns a 10-year-old girl studying in primary four. Her parents were very concerned about her behaviour at school. Her problem started in primary one when her class teacher commented that she was inattentive and restless. Assessment by a child mental health professional gave a negative result because the child behaved well in the assessment situation and the assessment showed that the child had very good intellectual abilities. As a result, the child was considered as gifted, and her inattentive and restless behaviour was seen as related to boredom in learning. However, the problem continued. Her parents were frustrated by her noncompliance in doing schoolwork. They had tried different parenting methods, including punishment, with no benefit. Consequently, the parent-and-daughter relationship became very strained.

A diagnosis of ADHD does not always lead to the use of medication. However, medication is proven to be effective with a large effect size, and is an important option for the treatment of ADHD.[1] In a study of ADHD treatment in four US communities, Jensen and colleagues found that only 12.5% of the children with ADHD had been treated with stimulant medication during the previous 12 months. Of those children who were prescribed stimulant medication, 50%

Figure 1. Differential diagnoses of disruptive behaviour



did not meet ADHD diagnostic criteria. Thus, both underprescribing and overprescribing of medication occurred.[2]

Overprescribing would stem from a false-positive diagnosis. The main causes of a false-positive diagnosis are the reliance on questionnaire results for diagnosis, or the reliance on the opinion of one person to make a diagnosis. The first vignette illustrates this problematic approach.

When considering the diagnosis of ADHD, one should always bear in mind the differential diagnoses of all kinds of disruptive behaviour as shown in Figure 1. The child in vignette 1 may be compatible with any of the differential diagnoses. In addition, these differential diagnoses could occur together with ADHD as coexisting conditions. Not recognizing the coexisting conditions may lead to unsuccessful treatment.

The opposite of overprescribing is equally harmful. It may mean that a child with ADHD, who may benefit substantially from medication treatment, continues to have difficulties in his/her brain functioning, leading to an impairment of his/her education, relationship and self-image. Vignette 2 illustrates this problem.

The following points are important considerations to prevent a false-negative diagnosis:

1. Parents who believe that the child is "naughty" may be unaware of the possibility of ADHD.
2. A clinician may believe that if a child behaves within normal limits in a clinical interview, then he/she does not have ADHD. However, a child with ADHD may behave within normal limits in a clinical interview for the following reasons:
   a. It is a novel situation;
   b. It is a one-to-one situation; or
   c. The interview may be too short.
3. A school teacher may not report inattentive or restless behaviour if:
   a. The class size is small so that the teacher can better manage the child's behaviour;
   b. The teacher is very tolerant and think that the child is still young;
   c. The teacher does not believe in the concept of ADHD;
   d. The child is intelligent and is not falling behind in schoolwork;
   e. The child is not the worst in behaviour when compared with other children in the class; or
   f. The school curriculum is not demanding.

Finally, the following three clinical vignettes would illustrate further diagnostic issues.

Vignette 3: An international school male student presented at the age of 14 with suicidal behaviour. When interviewed, he was anxious and depressed. A careful developmental history showed that he had ADHD of the inattentive subtype that was not recognized.

Vignette 4: A primary one student was diagnosed to have ADHD and showed initial improvement with medication treatment. After 3 months, her condition worsened again. Further assessment showed that she had dyslexia that had not been recognized.

Vignette 5: A 10-year old child presented with very impulsive and oppositional defiant behaviour at home. The possibility of ADHD was considered and medication treatment was tried, which made his condition worse. There was a major parenting problem with an overuse of punishment. There was also a serious rivalry with his younger brother. The diagnosis of ADHD was ruled out after a more careful assessment.

In summary, assessment of ADHD requires a careful developmental history with information from multiple sources. If the information does not match, then more time and consideration would be needed to make the diagnosis. The diagnosis of ADHD should always be followed by an assessment of other coexisting conditions. Vignette 4 illustrates this point. In difficult cases such as vignettes 3 and 5, assessment and treatment by more experienced clinicians will be required.

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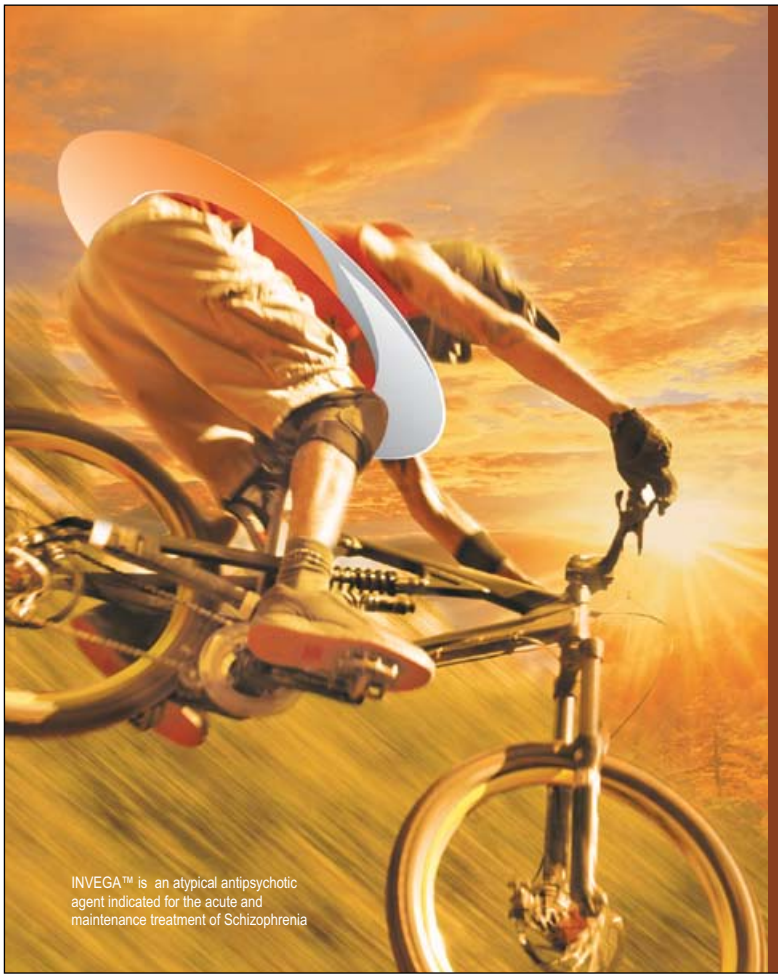

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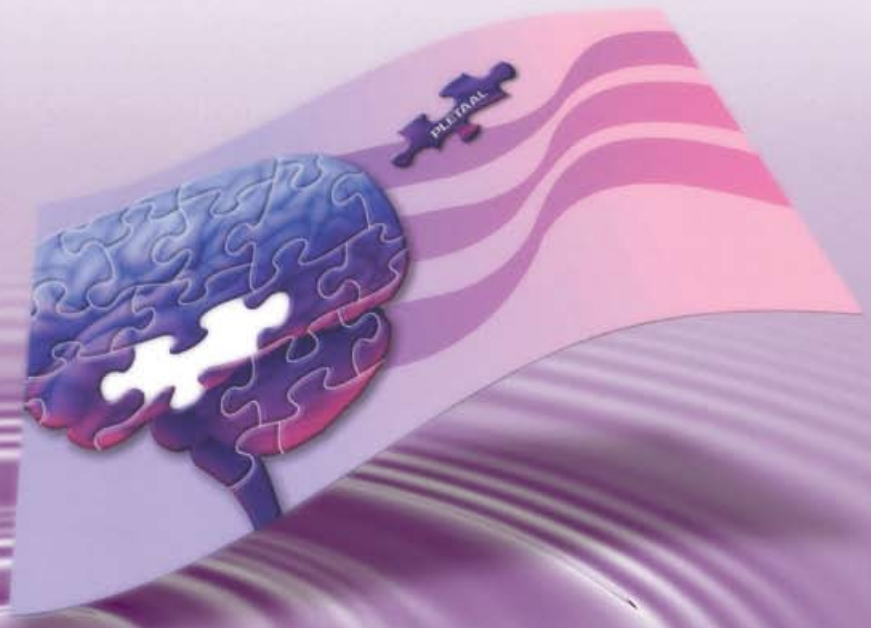

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