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¹ IMS Health December 2011

² HKAPI data December 2011

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Message from the President

In this issue, we highlight some common psychiatric conditions.

It has been found that people who suffer from mental illness have a high rate of comorbid physical health problems and a shortened life expectancy. For example, having conditions such as schizophrenia or bipolar disorder can lead to early mortality of about 20 years.

People who suffer from long-term physical conditions have very high rates of comorbid mental disorders, which are associated with worse outcomes, delayed recovery and longer hospital stay. Conditions such as diabetes, heart disease and chronic obstructive pulmonary disease cause higher rates of mental health problems (by about 30%), increasing health risk and delaying recovery. The risk of mortality for those with myocardial infarction is increased threefold if they suffer from comorbid depression.

Mental health disorder occurs in about 60% of acute hospital in-patients aged over 65 years old. Hence, there is a cogent call for all doctors, irrespective of their medical specialties, to understand both the physical and psychiatric components of their patients' illnesses and take appropriate steps to tackle them.

The last article by Dr Lee Yuk Tong highlights the latest development in endoscopic ultrasound. It will certainly worth your time to read this article and I wish to thank Dr Lee for sharing his experience with us.



Dr Lam Tat Chung, Paul
林達聰醫生

FRCP, FHKAM (Medicine)
FRCPsych, FHKAM (Psychiatry)
President

Pictorial Medical History (5)

Dr Lam Tat Chung, Paul (林達聰醫生)

FRCP, FRCPsych, FHKAM (Medicine), FHKAM (Psychiatry)
Specialist in Psychiatry (Private Practice)
Honorary Clinical Assistant Professor, The University of Hong Kong

According to legend, Asclepius was the son of Apollo and Coronis, one of Apollo's many lovers. On learning that Coronis had been unfaithful, Apollo had ordered her to be killed. As Coronis, pregnant with Asclepius, lay on her funeral pyre, Apollo had the child rescued. (This was the first legendary reported case of postmortem Caesarean section).

ASCLEPIUS TAKEN FROM THE WOMB OF CORONIS



Wood carving, 1549 edition of Alessandro Benedetti's *De Re Medica*

Depression and Chronic Physical Illness – Aiming for a Balanced and Integrated Approach



Professor Koen Demyttenaere

MD, PhD

University of Leuven, Belgium

Key words:

Depression (抑鬱症), chronic physical illness (慢性身體疾病), antidepressants (抗抑鬱藥), escitalopram (依他普侖)

Professor Demyttenaere started his lecture by noting the presence of somatic symptoms in depression. Sixty-nine percent of depressed patients may present with somatic symptoms as their chief complaints. Depression, anxiety and somatization may be seen in primary care patients, with comorbidity being more common than depression or anxiety alone. The presence of depression varies for different chronic physical illnesses; it ranges from 11% in Alzheimer's Disease to 51% in Parkinson's Disease. Depression also affects patient survival rates. Ten-year survival was reduced in patients with major depressive disorder (MDD) after stroke compared with

non-depressed stroke patients. Major depression dramatically increases mortality in patients with post-myocardial infarction, and is associated with obesity (increased BMI) and other changes which affect health (eg, increased smoking in diabetic patients).

Treatment of depression with antidepressants showed general efficacy in patients with physical illnesses. Selective serotonin reuptake inhibitors (SSRIs) have anti-platelet effects and thus offer additional benefits in depressed patients with cardiovascular disorders. There was modest efficacy of SSRIs in patients with myocardial infarction with depression or unstable angina with recurrent or severe depression. Small but significant benefits from SSRIs, tricyclic antidepressants (TCAs) and psychostimulants were observed in treating depression in post-stroke patients. In diabetes mellitus, antidepressants ameliorated depression but decreased glycaemic control and increased hypoglycaemia and food cravings. Consistent evidence of effectiveness for pharmacological treatment of depression has also been observed in cancer patients. A study found that antidepressants were effective in reducing depression in patients with rheumatoid arthritis, but otherwise no systematic reviews have been found for arthritis or osteoporosis. Escitalopram treats depression in post-stroke patients effectively, and it improves depression in patients with breast cancer, although not

as dramatically as in stroke. Escitalopram also has high efficacy and acceptability compared with other antidepressants, noted Professor Demyttenaere.

Patient compliance with medication may be a big problem. For example, baseline skepticism is associated with 62% increase in risk of discontinuation, while a positive attitude to medication gives better therapeutic effect of antidepressants. Depression is also a risk factor for noncompliance with medical treatments. Patients with low somatization tend to stay on antidepressants while patients with high somatization are associated with less drug compliance. Patient non-compliance may be monitored with Medication Event Monitoring System (MEMS) via recording of bottle opening. Having days missed is common; it is estimated that only 40% of patients follow their prescribed medication schedules all the time.

In summary, Professor Demyttenaere emphasized that depression may be at least as harmful as chronic physical illnesses. For many reasons, depression may not be prioritized as much but occurs surprisingly often in patients with chronic physical illnesses; it is also a risk factor for development of chronic physical illnesses. A balanced and integrated treatment approach to both conditions is likely to improve overall treatment outcomes, and antidepressants such as escitalopram can be effective regardless of comorbidity.

(Summary of talk presented at the Hong Kong Society of Biological Psychiatry Meeting held on 20 April 2013)

Comorbid Depression and Anxiety – Understanding and Treating Complex Patients



Professor Raymond Lam

MD, FRCPC

University of British Columbia, Canada

Key words:

Major depression (重度抑鬱症),
anxiety disorders (焦慮症),
comorbidity (合併症),
escitalopram (依他普侖)

As discussed in Professor Demyttenaere's lecture, comorbid depression and anxiety are common features in patients. Importantly, Professor Lam pointed out that depressed patients with comorbid anxiety have earlier age at onset, more severe depressive symptoms, increased suicidality (suicidal ideation), increased incidence of alcohol and drug abuse, more chronic course and longer time to first remission, more social distress and impairment in quality of life, poorer response to medication and higher healthcare utilization, compared with non-comorbid cases. Hence, early detection and treatment of anxiety disorders in complex patients are desirable, especially since they are associated with decreased risk for subsequent depression. Emotional symptoms are considered to be

more reliable for diagnosis compared with somatic symptoms. Effective treatments for anxiety disorders include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), benzodiazepines, pregabalin, buspirone, and irreversible monoamine oxidase inhibitors (MAOIs). For example, the SSRI escitalopram is licensed for treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), personality disorder (PD) and obsessive-compulsive disorder (OCD). Professor Lam noted that cognitive behavioral therapy (CBT) combined with drugs for panic disorder is a better treatment compared with CBT or drugs alone.

In the treatment of anxiety and depression comorbidity, Professor Lam emphasized the need for broad spectrum agents, the possibility that patients may experience side effects differently and may need dose and titration adjustments, and potential need for additional interventions such as CBT. Recommendations for maintenance treatment include:

- All patients should continue on antidepressants for 6 to 9 months after remission of symptoms
- Patients who require longer maintenance treatment (more than 2 years) include individuals with chronic episodes, severe episodes (suicidality, psychosis), difficult to treat episodes, frequent episodes (2 in 2 years, or 3 in 5 years), older age and/or comorbidity

For anxiety and depression comorbidity, long-term treatment is the rule, not

the exception. Optimal treatment must balance efficacy with tolerability.

As reviewed by Ali and Lam, escitalopram showed similar efficacy to SNRIs.¹ On the other hand, escitalopram demonstrated superior efficacy compared with citalopram and with SSRIs combined, and that efficacy differences may be modest but clinically relevant, especially in more severely depressed patients.¹ Specifically, pooled analyses of escitalopram in severe depression showed 6.1% to 14.3% more people in remission compared with other drugs. Escitalopram also had a lower rate of side effects compared with many other new antidepressants. Citalopram was noted to be cheaper but analysis showed that escitalopram was a better drug, in spite of cost, due to higher remission rates and cost-effectiveness. Based on pooled and meta-analysis studies, escitalopram was also better than paroxetine especially in subjects with high anxiety levels.

In summary, Professor Lam emphasized that patients with comorbidity present with complexities at a number of levels. In these patients, it is a challenge to define the primary condition in diagnosis; early treatment may improve prognosis which includes suicide and chronicity; treatment response is poor and may require combination therapy. Professor Lam recommended choosing treatments based on efficacy and tolerability, and utilizing clinical guidelines and individual patient profiles. The SSRI escitalopram has proven efficacy in MDD and a number of anxiety disorders.

Reference

1. Ali MK, Lam RW. *Neuropsychiatr Dis Treat* 2011;7:39-49.

(Summary of talk presented at the Hong Kong Society of Biological Psychiatry Meeting held on 20 April 2013)

Depression and Anxiety Scientific Symposium Series: Panel Discussion (HK Society of Biological Psychiatry, 20 April 2013)

Lexapro (escitalopram) has a generally favorable profile compared with other antidepressant drugs. With this in mind, the panel discussion started with the comments that the efficacy of Lexapro is not contested but some patients do have side effects (eg, palpitations at night or sleepiness). In addition, approximately 30–40% of patients have some sexual side effects, emotional detachment or nausea. Professor Demyttenaere mentioned good tolerability of escitalopram before discussing its sexual side effects. Professor Lam emphasized that there could be different reactions for specific patients. To minimize side effects, one may switch to a drug which is not a selective serotonin reuptake inhibitor (SSRI) and has a different side effect profile. Professor Lam encouraged more communication between doctors and patients; Professor Demyttenaere gave an example that if a patient has nausea,

it helps for the doctor to explain to the patient that it is a short term side effect. There is no habituation to sexual side effects, but sometimes escitalopram gets unfairly blamed for pre-existing problems.

Multiple comorbidities exist in many patients and anxiety maybe a component. Drug-drug interactions and the effect of SSRIs on serotonin's activation of the autonomic system may cause the side effects of SSRIs, which in turn can lead to drug non-compliance. It is important to tailor the dosage of SSRIs to individual needs. Drug regimen should also be simplified as this can increase drug compliance and reduce side effects.

Ethnic and cultural differences between patients in Hong Kong and America were also discussed during the panel session. Patterns of psychiatric illnesses may differ in the two regions. For example, Professor Lam mentioned differences in somatic versus emotional

expression of symptoms and also differences in drug metabolism with a higher percentage of Asians having delayed metabolism via the P450 2D6 enzyme. On the other hand, Professor Demyttenaere recommended a book on "the boredom of the self" for a discussion on the reasons our societies are so prone to depression.

Lastly, Dr Kwok discussed his management of a 90-year old patient who became depressed after a leg injury. Professor Lam suggested the use of electroconvulsive therapy since the patient has poor response to medications. Severe constipation and a history of stroke were also noted. SSRIs are known to affect platelet aggregation and this is important when assessing suitability of specific drugs for patient use. Benzodiazepines may cause problems for a 90-year old patient but otherwise may reduce anxiety. The conclusion was that many factors must be considered when treating depression.

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Abbreviated Prescribing Information:

Presentations: Quetiapine fumarate extended-release tablet. **Indications:** **Bipolar Disorder:** Maintenance treatment of bipolar I disorder; as monotherapy or in combination with lithium or sodium valproate, for the prevention of relapse/recurrence of manic, depressive or mixed episodes; Treatment of depressive episodes associated with bipolar disorder; Treatment of acute mania associated with bipolar I disorder as monotherapy or in combination with lithium or sodium valproate. **Schizophrenia:** Treatment of schizophrenia; prevention of relapse and maintenance of clinical improvement during continuation therapy. **Major Depressive Disorder:** Treatment of recurrent major depressive disorder (MDD) in patients who are intolerant of, or who have an inadequate response to alternative therapies. **Generalised Anxiety Disorder:** Treatment of generalised anxiety disorder (GAD). **Dosage:** **Schizophrenia:** Once daily in the evening. Initial dose: 300 mg (Day 1), 600 mg (Day 2) and up to 800 mg after Day 2. Range: 400-800 mg/day depending on clinical response & tolerability of patient. Same dosage is used for maintenance therapy. **Bipolar Disorder:** Acute Mania: Starting daily dose is: 400 mg (Day 1) & 600 mg (Day 2) & up to 800 mg (after Day 2), alone or in combination with a mood stabiliser. Range: 400-800 mg/day. **Bipolar Depression:** Starting dose is 50mg (Day 1) & 100 mg (Day 2) & 200 mg (Day 3) & 300 mg (Day 4). Titration can be up to 800 mg on Day 5 and up to 600 mg by Day 6. **Maintenance treatment:** Use same dose as active treatment for prevention of manic, depressive or mixed episodes in bipolar disorder. Range: 300-800 mg/day. **Recurrent major depressive disorder:** Once daily in the evening. Initial dose: 50 mg (Day 1 & 2), increased to 150 mg on Day 3 & 4. Usual effective dosage: 150 mg. Range of 50 - 300 mg/day. Same dosage is used for maintenance. **Generalised Anxiety Disorder:** Initial dose: 50 mg (Day 1 & 2), increased to 150 mg on Day 3 & 4. Range of 50 - 150 mg/day. **Switching from Seroquel XR:** Switch at equivalent total daily dose. Individual adjustments may be necessary. **Elderly or hepatic impairment patients:** Slower dose titration is recommended. Initial dose: 50 mg/day up to target dose depending on clinical response and tolerability of patient. In elderly MDD, initial dose: 50 mg (Day 1-3), increased to 100 mg (Day 4), 150 mg (Day 8) and then up to 300 mg (Day 1-3), increased to 100 mg (Day 4), up to 150 mg on day 8. **Renal impaired patients:** No dosage adjustment needed. **Contraindications:** Hypersensitivity to the active substance or excipients of this product. **Precautions:** Not recommended for below 18y old; clinical worsening and suicide risk associated with psychiatric disorders; somnolence; severe neutropenia; known cardiovascular & cerebrovascular disease; Conditions predisposing to hypotension; orthostatic hypotension; orthostatic symptoms; history of seizure; tardive dyskinesia; neuroleptic malignant syndrome; not approved in elderly patients with dementia-related psychosis; established diabetes mellitus; dyslipidaemia; jaundice development; venous thromboembolism; galactose intolerance; pregnancy & lactation. **Interactions:** CYP3A4 inhibitors; centrally acting drugs; grapefruit juice; thioridazine; tramadol; levodopa and dopamine agonists; carbamazepine; phenytoin; levetiracetam; ADHD medications & cardiovascular medicines that cause electrolyte imbalance or to increase QTc interval. **Undesirable effects:** Tachycardia; vision blurred; mild asthma; peripheral edema; irritability; increased appetite; dysarthria; elevations in serum transaminases (ALT, AST), syncope; thirst; abnormal dreams & nightmares and elevations in serum prolactin. **Full local prescribing information is available upon request. APLHK, XR010**

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Update of International Treatment Guidelines for Bipolar Disorder



Dr Lee Wing King (李永堅醫生)

FRC Psych (UK), FHKC Psych, FHKAM (Psych)

Specialist in Psychiatry

Key words:

Bipolar disorder (躁狂抑鬱症), international treatment guidelines (國際治療指引), hyperprolactinaemia (高催乳素血症), aripiprazole (阿立哌唑)

International Treatment Guidelines for Bipolar Affective Disorder

There are many international treatment guidelines for bipolar disorder, namely, the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society of Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013; United Kingdom (UK) National Institute for Health and Clinical Excellence (NICE) Guidelines, 2006; UK Maudsley Prescribing Guidelines, 2012; British Association for Psychopharmacology (BAP) Guidelines, 2009; CANMAT guidelines for the management of patients with bipolar disorder: update 2007; Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines, 2004;

American Psychiatric Association Practice Guideline, 2002; the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. These guidelines focused on the stepped care approach, acute and maintenance treatment of various phases of bipolar disorder, pharmacological treatment algorithms and psychological treatment options.¹⁻⁸

In this article, I am going to focus on the pharmacological treatment options for acute mania treatment and maintenance treatment of 3 guidelines including **CANMAT and ISBD collaborative guidelines, UK NICE Guidelines and UK Maudsley Prescribing Guidelines** (Table 1).

There are similarities and differences among these guidelines. Overall, UK NICE Guidelines 2006 may be a bit outdated among the 3 guidelines, and combination is in general well evidence-based and is the rule rather than the exception in treatment of bipolar disorder.⁹

For acute mania treatment, anti-psychotic (AP) medications and mood stabilizers were the main recommended treatment options in all 3 guidelines, though there were individual differences among the guidelines. CANMAT and ISBD collaborative guidelines 2013 offered the most comprehensive structured recommendations in 4 sections, compared with the other 2 guidelines. CANMAT and ISBD collaborative guidelines 2013 recommended monotherapy and combination therapy with lithium and valproate as first line treatment options. However, UK NICE Guidelines 2006 only recommended lithium and valproate

monotherapy treatment options. Benzodiazepines were recommended in UK NICE Guidelines 2006 and UK Maudsley Prescribing Guidelines 2012.

For maintenance treatment, atypical antipsychotics (AAPs) and mood stabilizers were the mainstay of treatment options. Again, CANMAT and ISBD collaborative guidelines 2013 offered the most comprehensive structured recommendations in 4 sections, compared with the other 2 guidelines. CANMAT and ISBD collaborative guidelines 2013 recommended monotherapy and combination therapy with lithium and valproate as first line treatment options. UK NICE Guidelines 2006 recommended monotherapy and combination therapy of lithium and valproate as first line and second line treatment options, respectively. Certain medications were commonly recommended in all 3 guidelines. For UK NICE Guidelines 2006, quetiapine and aripiprazole are now recommended as first line treatment options and valproate as second line treatment option. Notably, long term antidepressant monotherapy was not recommended in view of the possibility of manic switch. Long term use of first generation antipsychotics (FGAs) should be avoided due to the potential of depressive induction.

In addition, the World Federation of Societies of Biological Psychiatry (WFSBP) task force on treatment guidelines for the biological treatment of bipolar disorders update 2009 on the treatment of acute mania reviewed research evidence and categorized medications into 6 categories of evidence (A–F, A being the best), with recommendations graded from 1 to 5 (1 being the highest grade). The WFSBP task force put several antipsychotics (APs) and mood stabilizers

Table 1. Comparison of Guidelines on treatment options for acute mania treatment and maintenance treatment

	CANMAT and ISBD collaborative guidelines 2013	UK NICE Guidelines 2006	UK Maudsley Prescribing Guidelines 2012
Acute mania treatment	<p>1. First line:</p> <p>a. Monotherapy: lithium, divalproex, divalproex ER, olanzapine, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, asenapine, paliperidone ER</p> <p>b. Adjunctive therapy with lithium or divalproex: risperidone, quetiapine, olanzapine, aripiprazole, asenapine</p> <p>2. Second line:</p> <p>a. Monotherapy: carbamazepine, carbamazepine ER, Electroconvulsive therapy (ECT), haloperidol</p> <p>b. Combination therapy: lithium and divalproex</p> <p>3. Third line:</p> <p>a. Monotherapy: chlorpromazine, clozapine, oxcarbazepine, tamoxifen, cariprazine (not yet commercially available)</p> <p>b. Combination therapy: lithium or divalproex and haloperidol, lithium and carbamazepine, adjunctive tamoxifen</p> <p>4. Not recommended:</p> <p>a. Monotherapy: gabapentin, topiramate, lamotrigine, verapamil, tiagabine</p> <p>b. Combination therapy: risperidone and carbamazepine, olanzapine and carbamazepine</p>	<ol style="list-style-type: none"> Olanzapine Quetiapine Risperidone Lithium Valproate Carbamazepine Avoid valproate in women of child-bearing potential Use lithium only if symptoms are not severe because it has a slower onset of action than antipsychotics and valproate Short-term use of a benzodiazepine (such as lorazepam) in the initial management of acute behavioural disturbance or agitation 	<ol style="list-style-type: none"> Lithium 400 mg/d Valproate semisodium (starts at 250 mg tds) and slow release (starts at 50 mg/d) Aripiprazole 15 mg/d increasing to 30 mg/d as required Asenapine starts at 10 mg bd and reduces to 5 mg bd if necessary Olanzapine 10 mg/d increasing to 15 or 20 mg/d as required Risperidone 2 or 3 mg/d increasing to 6 mg/d as required Quetiapine IR (100 mg/d increasing to 800 mg/d as required) and XL (300 mg/d increasing to 600 mg/d on day 2) Haloperidol 5–10 mg/d increasing to 15 mg/d if required Lorazepam up to 4 mg/d Clonazepam up to 8 mg/d
Maintenance treatment	<p>1. First line:</p> <p>a. Monotherapy: lithium, lamotrigine (limited efficacy in preventing mania), divalproex, olanzapine, quetiapine, risperidone long-acting injectable (LAI), aripiprazole</p> <p>b. Adjunctive therapy with lithium or divalproex: quetiapine, risperidone LAI, aripiprazole, ziprasidone</p> <p>2. Second line:</p> <p>a. Monotherapy: carbamazepine, paliperidone ER</p> <p>b. Combination therapy: lithium and divalproex, lithium and carbamazepine, lithium or divalproex and olanzapine, lithium and risperidone, lithium and lamotrigine, olanzapine and fluoxetine</p> <p>3. Third line:</p> <p>a. Monotherapy: asenapine</p> <p>b. Adjunctive therapy: phenytoin, clozapine, ECT, topiramate, gabapentin, omega-3 fatty acids, oxcarbazepine, asenapine</p> <p>4. Not recommended:</p> <p>a. Monotherapy: gabapentin, topiramate, or antidepressants</p> <p>b. Adjunctive therapy: flupenthixol</p>	<ol style="list-style-type: none"> First line lithium, olanzapine, valproate Second line lithium with valproate, lithium with olanzapine, and valproate with olanzapine Use lamotrigine (especially if the patient has bipolar II disorder) or carbamazepine Quetiapine and aripiprazole can now be added as first line and valproate is now second line Treatment for at least 2 years and up to 5 years if the person has risk factors for relapse, such as a history of frequent relapses or severe psychotic episodes, comorbid substance misuse, ongoing stressful life events, or poor social support Antidepressants (selective serotonin reuptake inhibitors (SSRIs) are preferred) may be used in combination with a mood stabilizer to treat acute episodes of depression but should not be routinely used for prophylaxis Avoid long-term antidepressants Chronic or recurrent depression may be treated with an SSRI or Cognitive Behavioural Therapy (CBT) in combination with a mood stabiliser or with quetiapine or lamotrigine Combine lithium and valproate for the prophylaxis of rapid cycling illness 	<ol style="list-style-type: none"> First line Lithium, olanzapine, quetiapine and aripiprazole Second line Valproate, carbamazepine, lamotrigine, risperidone Always maintain successful acute treatment regimens (e.g. combination of mood stabilizer and atypical antipsychotic (AAP) among the above options) as prophylaxis Avoid long-term antidepressant

Adapted from references 1, 2, 3

Table 2. General recommendation for switching AP medications

Adverse effects	Suggested first choice APs	Other possible alternative APs
Acute EPS	Aripiprazole, olanzapine, quetiapine	Clozapine, risperidone (<4 mg/d), ziprasidone
Dyslipidemia	Aripiprazole, ziprasidone	
Impaired glucose tolerance	Amisulpiride, aripiprazole, ziprasidone	risperidone
Hyperprolactinaemia	Aripiprazole, quetiapine	Clozapine, olanzapine, ziprasidone
Postural hypotension	Amisulpride, aripiprazole, haloperidol, sulpiride, trifluoperazine	
QT prolongation	Aripiprazole (with ECG monitoring)	Low dose monotherapy of any drug not formally contraindicated in QT prolongation (with ECG monitoring)
Sedation	Amisulpride, aripiprazole, risperidone, sulpiride	Haloperidol, trifluoperazine, ziprasidone
Sexual dysfunction	Aripiprazole, quetiapine	clozapine
Tardive dyskinesia	clozapine	Aripiprazole, olanzapine, quetiapine
Weight gain	Amisulpride, aripiprazole, haloperidol, trifluoperazine	Quetiapine, risperidone, ziprasidone

Adapted from reference 3

including aripiprazole in the category of evidence A (with full evidence from controlled studies) and recommendation grade 1 (based on category A evidence and good risk-benefit ratio).⁸ These are the first choice medications.

APs are generally divided into FGAs and second generation antipsychotics (SGAs) – AAPs – according to their “date of birth”. In daily clinical practice, clinicians have to manage AP-induced side effects as APs have different tolerability/side effect profiles. FGAs mainly have side effects related to dopamine antagonism, namely, extrapyramidal side effects and hyperprolactinaemia. SGAs mainly have metabolic side effects, such as weight gain, impaired glucose tolerance, dyslipidemia and metabolic syndrome. Switching to other medications devoid of the side effects under concern is the usual recommended clinical practice. Combination of certain APs may also alleviate certain side effects.

General recommendation for switching AP medications³

There is evidence that both switching to and co-prescription of aripiprazole are effective in reducing weight gain, lowering prolactin and lipid levels in the blood, and reversing impaired glucose tolerance. The general recommendation for switching AP medications is shown in Table 2.

Treatment of AP-induced hyperprolactinaemia

Dopamine inhibits prolactin release, therefore, dopamine antagonists such as APs can be expected to increase prolactin plasma level via the tuberoinfundibular tract. Hyperprolactinaemia is often superficially asymptomatic. The degree of prolactin elevation is probably dose-related for all drugs. The consequences of hyperprolactinaemia include sexual dysfunction, menstrual disturbance, reduction in bone density, breast growth/galactorrhoea, suppression of hypothalamic-pituitary-gonadal

axis, and increased risk of breast cancer.

The propensity of APs causing hyperprolactinaemia is in this order: Risperidone > haloperidol > olanzapine > quetiapine > aripiprazole. The following is a summary of treatment procedures for AP-induced hyperprolactinaemia:

1. Treat symptomatic hyperprolactinaemia: sexual dysfunction, menstrual disturbance, reduction in bone density, breast growth/galactorrhoea, suppression of hypothalamic-pituitary-gonadal axis, and increased risk of breast cancer
2. Reduce dose of AP
3. Switch to a non-prolactin elevating drug: aripiprazole, clozapine, olanzapine, quetiapine, or ziprasidone
4. Add aripiprazole to existing AP: 3–6 mg per day; when switching, symptoms tend to resolve slowly (aripiprazole normalizes prolactin in those on haloperidol)
5. Add dopamine agonists (e.g. amantadine, cabergoline, or bromocriptine) to existing AP if it has to be continued but has a potential to worsen psychosis

Case Vignettes

Case illustration of management of AP-induced symptomatic hyperprolactinaemia side effect

Ms B is a 28-year-old clerk previously diagnosed with bipolar affective disorder in 2004, when she was only 19 years old. She presented with hypomanic symptoms, namely, elated mood, flight of ideas, increased goal-directed activities, reduced need for sleep, and talkativeness. She has no insight into her mental disorder, and was treated with risperidone (10 mg daily) and benzhexol (4 mg daily).

She developed hyperprolactinaemia-related side effects, namely, menstrual irregularities and galactorrhoea. Prolactin level was found to be 2,520 mIU/L. Brain CT scan was performed and no abnormality was detected. The patient was deemed to have AP-induced symptomatic hyperprolactinaemia side effects.

Haloperidol was switched to aripiprazole using the plateau switching method. The haloperidol dose was kept initially and aripiprazole was added and gradually titrated up to the therapeutic dose of 20 mg daily. Haloperidol was gradually tapered off to help minimize rebound phenomena when switching from other APs to an aripiprazole with little histaminic or cholinergic blockade and/or a long half-life. The patient remained in symptomatic remission and the menstrual irregularities and galactorrhoea side effects disappeared. Prolactin level went down to normal level.

Conclusion

There are many updated international evidence-based treatment guidelines for bipolar affective disorder and they focused on the stepped care approach, acute and maintenance treatment of various phases of the disorder, pharmaco-

logical treatment algorithms and psychological treatment options. These updated evidence-based international guidelines showed the efficacy of aripiprazole and some other APs in acute treatment of mania and maintenance treatment of bipolar disorder.

As different APs have different tolerability/side effect profiles, clinicians have to manage the AP-induced side effects in daily clinical practice. UK Maudsley Prescribing Guidelines, 2012 have clear evidence-based recommendations to guide clinicians to avoid the undesirable short-term and long-term consequences (may be irreversible) of these side effects and the consequential poor drug adherence and treatment effectiveness. There is evidence that both switching to and co-prescription of aripiprazole are effective in avoiding and managing AP-induced metabolic and endocrine side effects such as weight gain, hyperpro-

lactinaemia, dyslipidemia, and impaired glucose tolerance.

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References: 1. Berman RM et al. *J Clin Psychiatry*. 2007;68:843-853 2. Marcus RN et al. *J Clin Psychopharmacol*. 2008;28:156-165 3. Berman RM et al. *CNS Spectrum* 2009;14(4):197-206



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Reference: 1. Waites KB, Talkington DF. Mycoplasma pneumoniae and its role as a human pathogen. Clin Microbiol Rev. 2004 Oct;17(4):697-728. 2. Infectious Diseases Society of America/American Thoracic Society. Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007; 44: S27-S72. 3. Arnold FW et al. A worldwide perspective of atypical pathogens in community-acquired pneumonia. Am J Respir Crit Care Med 2007;175:1086-1093. 4. Hong Kong Prescribing Information.



Update on Clinical Applications of Endoscopic Ultrasound



Dr Lee Yuk Tong (李玉棠醫生)

MBChB, MD (CUHK), FRCP (Edinburgh, London), FHKCP, FHKAM (Medicine)

Specialist in Gastroenterology and Hepatology

Key words:

Endoscopic ultrasound (超聲波內視鏡), subepithelial tumour (黏膜下腫塊), pancreatic diseases (胰臟疾病)

Introduction

Endoscopic ultrasound (EUS) examination involves using a specifically designed echoendoscope in which a high frequency ultrasound (US) probe is incorporated at the tip of the modified endoscope (Figure 1). Alternatively, a miniature US probe can be inserted into the working channel of a standard medical endoscope (Figure 2) to perform the examination. The high-frequency US probe can provide high-resolution images of the organs surrounding the gastrointestinal (GI) tract and the mural structure of the gut wall. In addition, biopsy specimens can be obtained under real time using EUS-guided fine needle aspiration (FNA) (Figure 3). EUS was developed more than 30 years ago and has become an important tool in the diagnosis and staging of GI and lung cancers, and in guiding clinical management of various GI diseases.

Figure 1. Electronic radial echoendoscope (GF-UE260, Olympus Co., Ltd., Tokyo, Japan) can provide 360-degree cross-sectional images and Doppler study



Figure 2. Miniature ultrasound probe that can pass through the working channel of a standard endoscope for examination



“Lump and Bump” in the GI Tract

Submucosal bulging (or subepithelial tumour, SET) is a common endoscopic finding during routine endoscopic examination. It is estimated SET is diagnosed in every 300 routine endoscopic examinations.¹ Differential diagnoses, such as leiomyoma, gastrointestinal stromal tumour (GIST), ectopic pancreas, carcinoid tumour or extrinsic compression of the wall, are not easily established by endoscopy or even CT scan.²⁻⁴ EUS is able to clearly differentiate the 5- to 9-layered structure of the gut wall and has been shown to be highly accurate in predicting the nature of the SET.^{1,3,4} Through EUS-guided FNA, trucut biopsy and incisional biopsy, one can determine the malignant potential of the masses with an accuracy of up to 93%.⁵⁻⁶ Also, EUS

can guide selected use of endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) to remove the SET.⁷

Pancreatic Diseases

EUS has been shown to have a high sensitivity (93–100%) and accuracy in detecting pancreatic tumour diseases compared with CT and PET scans, particularly when the lesion is less than 2 cm in size.⁸⁻¹⁰ In a 26-year retrospective cohort study of Johns Hopkins Hospital, EUS was found to be significantly more sensitive than CT scan in detecting pancreatic neuroendocrine tumours, especially insulinomas (84.2% vs 31.6%).¹⁰ In patients with abnormal findings on routine radiological examination, EUS can confirm or rule out the presence of pancreatic lesions. In a retrospective study of 213 patients with a

Figure 3. Electronic linear echoendoscope (GF-UCT260, Olympus Co., Ltd., Tokyo) that can guide FNA and different endoscopic interventions



focal lesion on CT scan/MRI but without obstructive jaundice, EUS and FNA identified 173 lesions, which equates to an accuracy of 97.6%, sensitivity of 96.6%, specificity of 99%, negative predictive value (NPV) of 96.2% and positive predictive value (PPV) of 99.1%.¹¹ Overall, 39 patients were negative for pancreatic disease and no lesions were found during long-term follow up.¹¹ In another retrospective review of 32 patients with suspected pancreatic cancer but without lesions on CT scan, EUS identified 74% of the underlying diseases correctly giving a PPV of 86% and an NPV of 63%.¹² Combining EUS and FNA can improve the diagnostic yield in these patients. In a recent meta-analysis of 41 studies, EUS-FNA demonstrated a pooled sensitivity of 86.8%, pooled specificity of 95.8%, positive likelihood ratio of 15.2 and a negative likelihood ratio of 0.17 in diagnosing the correct aetiology of

versus 6 months of the group of patients who had not undergone EUS. This was probably related to the use of appropriate stage-dependent treatment strategies.¹⁵ For patients with unresectable pancreatic cancer, EUS-guided celiac plexus neurolysis (CPN) is effective in reducing morphine requirement. However, the CPN should be done in the early stages of the disease before the pain memory is established.¹⁶

With its high sensitivity in detecting early and small pancreatic cancer, EUS is used in screening high-risk patients. They include those with strong family history of pancreatic cancer disease and those with certain genetic diseases, such as Peutz-Jeghers syndrome and hereditary non-polyposis colorectal cancer diseases.¹⁷

For pancreatic cystic lesions, EUS-FNA of the cystic fluid (for analysis of CEA and amylase levels) together with cytology examination, could differ-

entiate between benign (eg, serous cystadenoma) or potentially malignant lesions (eg, mucinous cystadenoma or intraductal papilla mucinous tumour).¹⁸ For patients unfit for surgery, EUS-guided ethanol and paclitaxel ablation of pancreatic cysts is effective in reducing the size, or even eradicating the cystic lesion.¹⁹

Acute fluid collection, pseudocyst formation and necrosis are common in patients with severe acute pancreatitis, and are usually treated by surgical drainage. Recent studies had shown minimally invasive methods such as endoscopic or percutaneous drainage and necrosectomy could improve patient outcomes, including complication and mortality rates.²⁰⁻²¹ Long-term follow-up studies have also shown that patients treated with minimally invasive methods tend to have less endocrine and exocrine deficiency. Additionally, EUS-guided fluid aspiration and pseudocyst drainage was shown to achieve higher success rate than non-EUS guided method.²²

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Biliary Obstruction

Endoscopic retrograde cholangiopancreatography (ERCP) was once considered the gold standard in the diagnosis of biliary obstructive diseases, such as common bile duct (CBD) stone. However, the invasiveness of the procedure limits its use for routine diagnostic purposes. Furthermore, studies had shown that small stones or sludge disease could be missed during ERCP if sphincterotomy is not performed.²³ EUS had been shown to have higher sensitivity, PPV and NPV (>95%) in diagnosing CBD stone than

ERCP or MRCP. The accuracy of EUS would not be affected by the bile duct size and stone size;²⁴ however, if the CBD stone size is below 5 mm, the sensitivity of MRCP may drop to 61%.²⁵ Using EUS as a triage tool for screening patients suspected of having CBD stone, more than 75% of unnecessary ERCP and its related complications can be avoided.²⁶ A meta-analysis of four related studies had confirmed the benefit of EUS-guided ERCP approach in patients suspected to have biliary obstruction.²⁷

Lung Cancer Staging

Lung cancer is the number one cancer killer in Hong Kong. Management of lung cancer relies heavily on cancer staging, particularly on the status of mediastinal lymph nodes (MLN). In the past, mediastinoscopy was the gold standard for confirming the presence of MLN metastases; however, it is associated with certain morbidities, including bleeding and recurrent laryngeal nerve palsy in 1–2% of patients. Furthermore, mediastinoscopy may not be able to cover all mediastinal lymph node stations, particularly distal paraoesophageal lymph node stations.

Transoesophageal EUS is shown to have a high sensitivity in detecting the presence of MLN. The presence of MLN metastases can be confirmed by EUS-FNA. A meta-analysis of 76 studies reported that the pooled sensitivity and pooled specificity of EUS were 88% and 96.4%.²⁸

In a local study of 125 patients with MLN diseases, EUS-FNA confirmed and excluded malignancy in 50% and 34% of the patients, demonstrating sensitivity, specificity, PPV, NPV and accuracy of 75%, 100%, 100%, 67% and 83%, respectively. Overall, 69% of the patients changed their initial plan for invasive investigations and surgery after EUS-FNA.²⁹ The introduction of endobronchial ultrasound (EBUS) further expands the role of endoscopic MLN staging (so called “medical mediastinoscopy”). EUS- and EBUS-FNA are highly recom-

mended staging methods for confirming the presence of MLN metastases before deciding on treatment. Both the American and European thoracic society guidelines recommend this approach before using the more invasive mediastinoscopy approach.³⁰ Direct surgery would not be appropriate in cases of MLN metastases. This group of patients should undergo chemotherapy or radiotherapy before surgery to improve survival.

Both the American and European Thoracic Society guidelines recommend EUS/EBUS-FNA before using the more invasive mediastinoscopy approach

Biliary Intervention

Recent technological advances have enabled EUS-guided intervention to access the bile duct and gallbladder. EUS-guided hepaticogastrostomy, choledochoduodenostomy and cholecystoduodenostomy all allow for an alternative route of internal drainage in patients unsuitable for surgical or percutaneous drainage. The success rate is between 75%–100%. Other EUS-guided therapies under development include radiofrequency ablation of pancreatic cancer, fiducial placement before targeted radiotherapy, and cytoimplant injection to treat advanced stage pancreatic cancer.

Conclusion

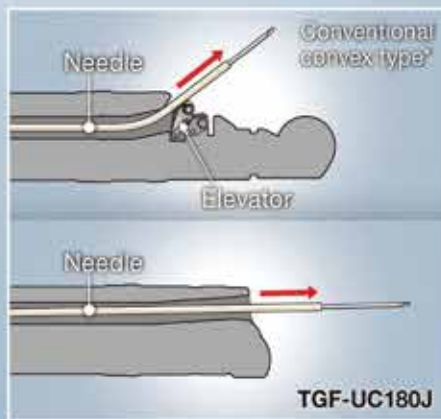
EUS is an integral part of investigation and treatment in the clinical management of various GI and pulmonary diseases. The efficacy of EUS examination depends on the echo-endoscopists’ experiences in accurate image interpretation and performing imaging-guided therapy.

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13:00 - 14:00 Registration & Buffet Lunch
14:00 - 14:30 **Functional Food & Gastrointestinal Disease: Snake Oil for the New Millennium?**
Professor Geoffrey Cleghorn
Director of Research & Professor of Paediatrics, University of Queensland, Australia
14:30 - 15:00 **Impact of Gangliosides and DHA on Early Childhood Cognitive Development**
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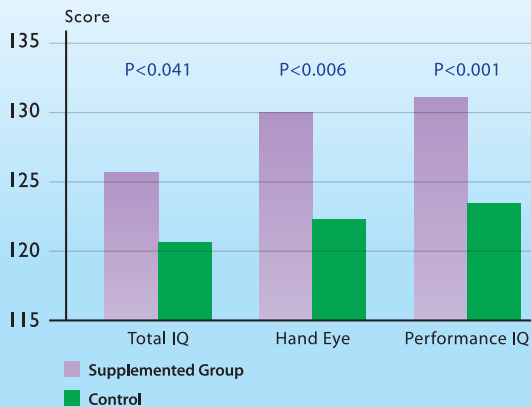


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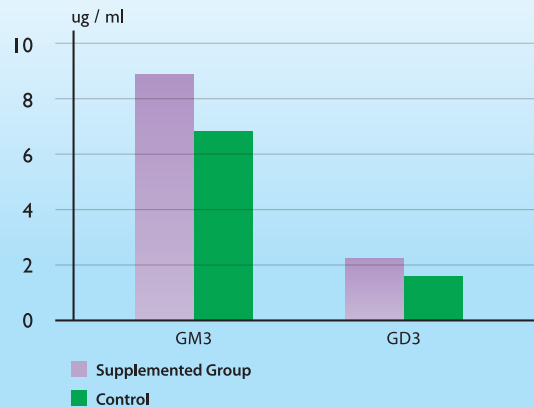
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