



Regional Update

Consensus statements on adherence issues in schizophrenia for Hong Kong



K.Y. Mak^{a,*}, W.T.L. Lo^b, W.S. Yeung^c, Michael Wong^d, W.S.D. Chung^e, E. Chui^d,
Ka-Lok Tam^f, L.K. Hui^g, Jolene Mui^h, O.W. Chanⁱ, K.L. Wong^d

^a Room 704, Alliance Building, 130-136 Connaught Road Central, Hong Kong

^b Kwai Chung Hospital, Kwai Chung, Hong Kong

^c Department of Psychiatry, Pamela Youde Nethersole Eastern Hospital, Hong Kong

^d Department of Psychiatry, Queen Mary Hospital, Hong Kong

^e Tai Po Hospital, Hong Kong

^f Department of Psychiatry, United Christian Hospital, Hong Kong

^g Department of Psychiatry, Kowloon Hospital, Hong Kong

^h Castle Peak Hospital, Hong Kong

ⁱ Hong Kong Hospital Authority, Hong Kong

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ABSTRACT

Aim: In view of the clinical importance of the adherence issues in schizophrenia management, a consensus group of experienced local psychiatrists and nurse specialists gathered to outline a number of consensus statements for clinicians to consider enhancing adherence in their patients.

Process: Prior to the consensus group meeting, three core members drafted eight statements on the issue of adherence in schizophrenia. Using a modified Delphi method, published literature and published guidelines regarding the management of schizophrenia were reviewed by the full panel during the group meeting. After discussion and reflection from each individual member of the consensus group, the eight statements were reworded and electronically voted on anonymously in two steps: acceptance on quality of evidence and practicability in implementation.

Results: After modifications of the original statements, there was very high overall level of agreement and acceptance (reaching international standard) on all the five areas of adherence within the eight statements of the finalised statement.

Conclusions: The present consensus statements are the first in Hong Kong to address systematically adherence issues in schizophrenia management. They include areas on adherence assessment and definition, treatment strategies in enhancing adherence, and treatment considerations at specific phases of schizophrenia. They are tailored to be of practical utility in the local Hong Kong setting.

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1. Introduction

Adherence to treatment is essential for patients with schizophrenia to achieve clinical remission. Despite the availability of new drugs with improved efficacy and safety profiles, poor adherence remains a major issue in schizophrenia (Masand et al., 2009). Studies have shown that up to 20–40% of patients with schizophrenia fail to adhere to treatment (Chen et al., 2010; Valenstein et al., 2006), and poor adherence may have significant impact on the clinical outcome of patients, leading to psychiatric

complications, treatment resistance, and increased risk of relapse, comorbidities or even suicide (Masand et al., 2009). As a result, adherence should be assessed accurately and regularly so that measures can be readily implemented in case of lack of adherence.

In Hong Kong, clinicians often fail to detect non-adherence (Hui et al., 2006). There is no standardised procedure for the regular assessment of patient adherence. Standardised treatment regimens in enhancing adherence are also lacking. In view of this, a consensus meeting was organised in Hong Kong as an attempt to develop a local consensus to enhance adherence in the treatment of schizophrenia, including proper clinical assessment, use of long-acting injectable antipsychotics (LAIs), and various psychosocial interventions. The essence of the consensus statements is to provide a review of current knowledge and opinions concerning

* Corresponding author. Tel.: +852 2815 5111; fax: +852 2850 6556.
E-mail address: kymak@hku.hk (K.Y. Mak).

the management of schizophrenia. The foundation of the statements is evidence-based medicine, but interpretive comments from the consensus group based on their expertise were provided to back up the statements in case of inadequate or contradictory evidence (Couetil et al., 2007). Comments from the consensus group on the statements are also key to identify research gaps to guide future research.

2. Methods

A meeting was held on 23rd July 2013 in Hong Kong, and the consensus group included council members of the Hong Kong Association of Psychosocial Rehabilitation and local clinical healthcare professionals experienced in the management of schizophrenia. Prior to the meeting, three core members of the consensus group, based on clinical experience on the issue and literature search, drafted 8 consensus statements. Five areas were identified as important and relevant, viz.: (1) adherence assessment; (2) defining adherence; (3) pharmacological interventions; (4) psychosocial interventions; and (5) treatment considerations at specific phases of illness. The literature search was performed using the PUBMED database with the following keywords: 'schizophrenia and adherence', 'atypical antipsychotics and adherence', and 'psychosocial intervention and adherence'. Only those papers published after 2000 were included, and reports that specifically address the adherence issue in schizophrenia were included.

The modified Delphi method (Leung et al., 2013; Linstone and Turoff, 2002) was abbreviated and employed for the formal face-to-face expert focus 'consensus group' meeting. First, the core members took turns to present the statements along with the associated research evidence. After a comprehensive review and free discussion, all (eleven) members of the consensus group voted anonymously on each statement using electronic voting devices. With reference to the methodology used by Ooi et al. (2010), each statement was rated according to both (1) classification of recommendation (based on good, fair or poor scientific evidence to support or refute the statement), and (2) practicability of recommendation in Hong Kong (accept or reject with or without reservation). A consensus statement was only accepted if at least 80% of the participants voted "A" or "B" for classification of recommendation, and at least 65% voted "A" or "B" for practicability (Table 1).

3. Results

After discussion, all eight consensus statements were finalised and accepted by the consensus group. The statements were categorised into five major parts. The first two parts (statements

1–4) focused on the predictors, assessment and definition of adherence, laying a foundation before addressing pharmacological and psychosocial interventions for adherence in Parts 3 and 4 (statements 5–7). Part 5 (statement 8) addresses treatment strategies at different phases of the course to enhance adherence and clinical outcome of schizophrenia.

3.1. Adherence assessment

3.1.1. Statement 1: Patients with multiple complex predictors should be identified as having a risky profile for non-adherence

Voting on

1. Classification of recommendation: A-55%, B-45%, C-0%, D-0%, E-0%
2. Practicability of recommendation: A-36%, B-55%, C-9%, D-0%, E-0%

After reviewing the various major references (Hui et al., 2006; Oehl et al., 2000; Valenstein et al., 2006; Velligan et al., 2009), it was agreed that 'medication adherence' is associated with four main factors, which may be characterised as patient-, physician-, treatment-, and environment-related (Oehl et al., 2000). Patient-related factors mainly refer to demographic parameters. For instance, patients of young age and male gender, patients with comorbidities such as substance abuse and mood symptoms, and patients with lack of formal education and poor illness insights are more likely to be non-adherent (Hui et al., 2006; Valenstein et al., 2006; Velligan et al., 2009). Health beliefs in terms of patients' perceptions towards antipsychotic medication, subjective wellbeing and quality of life are also correlated with adherence (Oehl et al., 2000; Velligan et al., 2009). Physician-related factors including therapeutic alliance and having a well-structured treatment plan have an important impact on adherence; whereas treatment-related factors including the benefit/risk ratio of medication and route of administration, and environment-related factors such as the level of family/social support are also associated with the level of adherence (Oehl et al., 2000; Velligan et al., 2009).

In Hong Kong, previous local studies exploring antipsychotic adherence in patients with schizophrenia concluded that predictors of non-adherence included awareness of illness, attitudes towards treatment, perceived benefits of medication, younger age, prescription with clozapine, and symptom severity (Bressington et al., 2013a). It is therefore important that healthcare professionals be advised to take note of patients' medical history and their clinical/emotional status throughout the course of illness, as well as supervise their treatment

Table 1

The grading system for each consensus statement during the voting session.

Quality of evidence	Classification of recommendation	Practicability of recommendation
I: Evidence obtained from at least 1 randomised controlled trial	A: There is good evidence to support the statement	A: Accept completely
II-1: Evidence obtained from well-designed control trials without randomisation	B: There is fair evidence to support the statement	B: Accept with some reservation
II-2: Evidence obtained from well-designed cohort or case-control study	C: There is poor evidence to support the statement but recommendation made on other ground	C: Accept with major reservation
II-3: Evidence obtained from comparison between time or places with or without intervention	D: There is fair evidence to refute the statement	D: Reject with reservation
III: Opinion of respected authorities, based on clinical experience and expert committees	E: There is good evidence to refute the statement	E: Reject completely

Modified from the Canadian Task Force on the Periodic Health Examination [Barkun], Ooi et al. (2010).

programmes, in order to assess whether they are at risk of non-adherence. The consensus group also considered ranking the risk factors for non-adherence using a hierarchical approach according to clinical practice.

3.1.2. Statement 2: Validated adherence rating scales should be employed to assist the assessment of patient adherence in daily clinical practice

Voting on

1. Classification of recommendation: A-36%, B-55%, C-9%, D-0%, E-0%
2. Practicability of recommendation: A-73%, B-27%, C-0%, D-0%, E-0%

After reviewing related references (Kane, 2007; Velligan et al., 2006, 2009), it was agreed that 'assessment of adherence' may be direct or indirect. Direct methods include observation of medication intake and measurement of plasma drug levels and biological markers. However, direct methods are burdensome and impractical in routine clinical practice. Alternatively, adherence may be assessed using indirect methods, which include patient self-report and diary, pill counts, prescription refill data, and electronic monitors (Kane, 2007). In particular, patient self-report in the form of rating scales is an efficient and cost-effective method of assessing adherence (Thompson et al., 2000; Velligan et al., 2009). They are also regarded as easy to use (Velligan et al., 2009), requiring a relatively short time to complete.

There are a number of commonly used adherence rating scales, including the Drug Attitude Inventory (DAI) (Hogan et al., 1983; Thompson et al., 2000), the Medication Adherence Rating Scale (MARS) (Thompson et al., 2000), and the Brief Adherence Rating Scale (BARS) (Byerly et al., 2008). The DAI is the most commonly used instrument that contains 10/30 items focusing on subjective attitudes towards antipsychotics; it has good internal consistency. The MARS is a 10-item self-report inventory which was based on the DAI and the BARS is a clinician-administered adherence instrument demonstrating good sensitivity and specificity in identifying non-adherent outpatients.

All three scales have been validated with sound psychometric properties, and they represent most of the components required in the assessment of adherence. However, drawbacks on the use of scales may include the potential to exaggerate the degree of adherence (Velligan et al., 2006), and reduction of patients' motivation to receive continuous drug therapy. After further discussion, the consensus group agreed that in order to reflect the true level of adherence accurately, clinical judgement and other direct/indirect methods should be included.

3.2. Defining adherence

3.2.1. Statement 3: The percentage of medication taken over a period of time should be considered as a useful way of defining adherence

Voting on

1. Classification of recommendation: A-36%, B-46%, C-18%, D-0%, E-0%
2. Practicability of recommendation: A-55%, B-36%, C-9%, D-0%, E-0%

So far, there is no clear consensus in the literature regarding the definition of medication adherence (Masand et al., 2009; Patel and David, 2007; Velligan et al., 2006). Nonetheless, the percentage of medication taken over a period of time seems to be the most pragmatic method in defining adherence (Velligan et al., 2009).

Medication gaps during which no medication is taken by the patient during a time period can also be used to assess adherence, but dichotomised adherence scores (e.g. cessation of medication, adherent/non-adherent) should be avoided if possible (Velligan et al., 2009). Patients' attitude towards medications is not a widely supported method of defining non-adherence (Velligan et al., 2009).

The group concluded that in terms of the definition of "period" over which medication adherence should be assessed, the finite length of a month or the follow up interval of clinical contact can be used as the unit of time. Nevertheless, the interval of follow up contacts may depend on the patients' condition.

3.2.2. Statement 4: Definition of full, partial and non-adherence should be cut-off as >80%, 50–80% and <50% of total prescribed medication taken respectively

Voting on

1. Classification of recommendation: A-18%, B-64%, C-18%, D-0%, E-0%
2. Practicability of recommendation: A-45%, B-45%, C-9%, D-0%, E-0%

Adherence is often reported as an all-or-nothing behaviour, and clinicians tend to focus on non-adherent patients and often underestimate the issue of partial adherence (Masand et al., 2009). After reviewing the various references (Oehl et al., 2000; Velligan et al., 2009; Weiden et al., 2004), the group preferred the definition on 'partial adherence' as a patient taking some, but not all, of the prescribed medication (Weiden et al., 2004), since in reality, instead of complete discontinuation of treatment (non-adherence), a majority of patients tend to be partially adherent to treatment at any point in time.

The percentages regarding the level of adherence were derived from an earlier expert consensus involving a panel of over 40 global clinical experts. The 80% cut-off (for good adherence) is consistent with that adopted in major research studies and reviews (Patterson and Leeuwenkamp, 2008; Valenstein et al., 2006; Velligan et al., 2009).

3.3. Pharmacological interventions

3.3.1. Statement 5: Patients with adherence issue should be given informed choice including long acting injectable atypical antipsychotics

Voting on

1. Classification of recommendation: A-45%, B-55%, C-0%, D-0%, E-0%
2. Practicability of recommendation: A-64%, B-36%, C-0%, D-0%, E-0%

The group opined that because of the importance of medication adherence to the disorder, patients should be educated, and as far as possible, given the informed choice of different types of treatment, including long-acting injectable antipsychotics (LAIs). According to the references, the potential benefits of LAIs in addressing adherence issue include assurance of medication delivery, leading to the immediate recognition of non-adherence and clear appraisal of relapse that occurs despite adequate pharmacotherapy. Other advantages include the encouragement of regular contacts between patients and clinicians, convenience for patients, achieving consistent plasma drug levels, and continued medication coverage after a missed dose (Kane, 2006; Nasrallah and Lasser, 2006; Patel et al., 2009; Rainer, 2008; Zhornitsky and Stip, 2012).

Table 2
Adherence rate of different antipsychotics in patients with schizophrenia (Lambert and Singh, 2006; Olivares et al., 2009).

Antipsychotics	Percentage of patients who stayed on medications
Oral	63.4%
Typical	34.0%
Risperidone	51.4%
Olanzapine	71.0%
Clozapine	81.3%
Conventional LAIs	65.3%
Risperidone LAI	81.8%

In Hong Kong, however, there are a number of limitations of LAIs resulting in a relative low usage rate (<40% and <10% of all schizophrenic patients receive conventional depot injections and atypical LAIs respectively). According to the panel, this is because the patients' conception that injections are only reserved for difficult-to-treat illness; the relatively high cost of atypical LAIs; a sense of lack of self-control over medications; pain at the injection site; and the doctors' perception of the difficulty in dose titration due to the long waiting time with delayed drug release (Kane, 2006; Patel et al., 2009; Taylor, 2009; Zhornitsky and Stip, 2012).

According to the data available (Haddad et al., 2009; Olivares et al., 2009; Taylor, 2009), although LAIs may still exhibit similar side-effects as oral antipsychotics such as extrapyramidal symptoms, prolactin-related adverse events, increased body weight and body mass index, etc. (Buchanan et al., 2010; Fleischhacker, 2009; Rossi et al., 2012), the use of LAIs over oral medications nonetheless has been supported by global data indicating that a

generally greater proportion of patients receiving LAIs stay on treatment (Table 2) (Lambert and Singh, 2006; Olivares et al., 2009).

With the recent available information on atypical LAIs, it was agreed by the consensus group that atypical LAIs are more effective than typical LAIs, with the latter better than oral atypicals which are usually more effective than oral typicals. Therefore, the consensus group concluded that LAIs should be considered a treatment option for patients with adherence issues, as they can facilitate adherence reducing the risk of relapse, not to mention that there are indeed some patients who prefer injectable therapy (Nasrallah and Lasser, 2006).

Nevertheless, not every patient will accept injectable therapy, as a survey showed that about 30% of patients with schizophrenia totally refused depot treatment (Heres et al., 2007). It is noted that more exposure to LAIs may help increase patients' confidence in using LAIs (Heres et al., 2007). Therefore, the consensus group acknowledged that patient preference is an important factor in the choice of treatment options, and psychiatrists are obliged to assist their patients in making the right decision.

3.3.2. Statement 6: LAI atypical antipsychotics should be considered as an option among indicated patients early in the course of illness in improving adherence

Voting on

1. Classification of recommendation: A-27%, B-64%, C-9%, D-0%, E-0%
2. Practicability of recommendation: A-36%, B-55%, C-9%, D-0%, E-0%

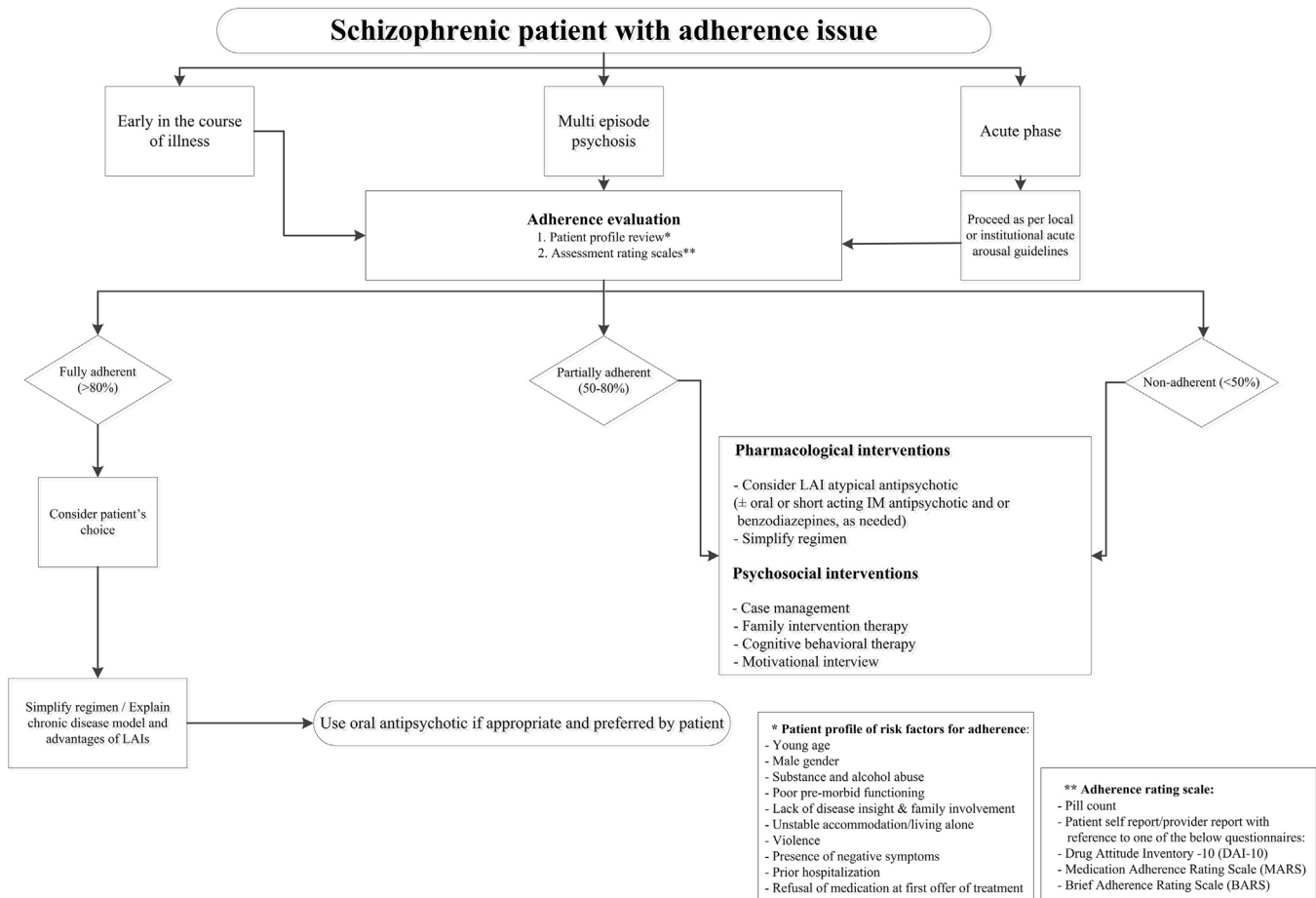


Fig. 1. Clinical expert advice for management of schizophrenic patients with adherence issue.

According to the literature (Hill et al., 2010; Kim et al., 2012; Perkins et al., 2008; Subotnik et al., 2011), non-adherence is a significant health concern in patients with early psychosis, and studies have shown that nearly 60% of such individuals become non-adherent after one year (Perkins et al., 2008). The reason for the high non-adherence rates includes the notion that recovering patients with early psychosis may not recognise the importance of maintaining treatment and may therefore discontinue treatment prematurely (Perkins et al., 2008). A recent clinical review on the management of schizophrenia recommended that in patients with early psychosis who demonstrate a poor adherence risk profile (Fig. 1), LAI atypical antipsychotics should be considered as a treatment option in the early course of the disorder (Newton et al., 2012). An open-label trial showed that the non-adherence rate in patients receiving risperidone LAI is low, with over 70% of patients completing treatment (Chue and Emsley, 2007).

During the discussion, it was pointed out that the relapse rate within five years of the first onset of illness is very high (Robinson et al., 1999). Those with comorbid substance abuse problems or with other “high-risk” factors (such as impulsive or violent behaviour during relapses) may also benefit from LAI treatment (see Fig. 1). However, this latter point was based more on expert opinions, and further evidence-based medicine is required to support this conclusion.

The consensus group opined that the use of LAIs to enhance adherence is not widely adopted during the early course of schizophrenia in Hong Kong, as adherence in the long-term outcome may not be considered as an important issue at this early stage of the disorder. Presently many clinicians will only consider prescribing LAIs when early-phase patients refuse to take oral medications. Some will use LAIs when their patients engage in disruptive behaviours which may present a danger to society. Therefore, the consensus group agreed that clinicians should alter their attitudes regarding LAIs as reserved only for chronic patients or those with multiple relapses, and that LAIs should not be considered as a punishment or deterrent treatment for dangerous behaviour in acute patients. Actually, the use of LAIs in the early course of illness may have significant benefits over oral antipsychotics (Emsley et al., 2008). Nevertheless, such opinion on the advantages of using LAIs in the early course of schizophrenia requires more concrete local evidence.

3.4. Psychosocial interventions

3.4.1. *Statement 7: Adjunctive psychosocial interventions should be considered to be an integral part of the personalised care package to improve adherence*

Voting on

1. Classification of recommendation: A-82%, B-18%, C-0%, D-0%, E-0%
2. Practicability of recommendation: A-82%, B-18%, C-0%, D-0%, E-0%

According to the literature, there are different forms of psychosocial interventions that can be applied in the treatment of schizophrenia, such as cognitive-behavioural therapy, family therapy, social skills training, and cognitive remediation (Adams et al., 2000; Bustillo et al., 2001; De Silva et al., 2013; Dixon et al., 2009; Patterson and Leeuwenkamp, 2008). Supportive psychosocial therapies may help alleviate residual symptoms and improve social functioning and quality of life; and improved clinical outcome in turn can encourage patients to adhere to treatment. An important example is the randomised controlled trial when patients with early psychosis were treated with antipsychotics plus 12 months of psychosocial intervention, and the results

showed a significantly lower risk of treatment discontinuation than those treated with antipsychotics alone (Guo et al., 2010). Another major randomised controlled trial demonstrated that a significantly greater proportion of patients with early psychosis using the integrated treatment approach (pharmacotherapy, psychosocial treatment, and psychoeducation) were adherent to drug treatment when compared with those treated with antipsychotics alone (Valencia et al., 2012).

Cognitive behavioural therapy and coping skills training are also considered effective since they specifically target the patient's perspectives of the illness and medication (Patel and David, 2007). Besides, combining pharmacotherapy and psychosocial interventions should be considered an integral part to improve adherence. However, the consensus group opined that each form of psychosocial therapy does vary in its therapeutic function, and should thus be tailored to the individual patient.

3.5. Treatment considerations at specific phases

3.5.1. *Statement 8: Phase-specific review of treatment regimes should be conducted regularly for patients with adherence issue*

Voting on

1. Classification of recommendation: A-55%, B-45%, C-0%, D-0%, E-0%
2. Practicability of recommendation: A-91%, B-9%, C-0%, D-0%, E-0%

On the whole, the consensus group accepted that there should be different treatment strategies for different phases of schizophrenia. Presently, there is a trend that doctors used the same medications (with adjustment in dosage) throughout the whole course of the disorder, disregarding the physical and mental conditions of their patients, or the potential long-term side effects of the medications.

In the acute phase, the major goals are to control psychotic symptoms and reduce agitation (Lehman et al., 2004). It is important that before prescribing the first medication, clinicians should review the medical histories and clinical status of their patients. During this phase, dosing of antipsychotics may be titrated as quickly as tolerated to the target therapeutic dose (Lehman et al., 2004). It has also been suggested that the use of adherence therapy (combining motivational and cognitive behavioural techniques) just after an acute episode can be promising in modifying patients' beliefs about treatment to enhance medication adherence (Schulz et al., 2013).

In the stabilisation phase, treatment should focus on reducing the risk of relapse, supporting patients to resume a normal life, and promoting the process of recovery. During this phase, the additional use of supportive psychosocial interventions can be less directive and more recovery oriented than in the acute phase.

For the stable or maintenance phase, the goal is to sustain remission and improve patients' quality of life. Regular monitoring of adverse events and the use of antipsychotics that substantially reduce the risk of relapse are recommended during this phase (Lehman et al., 2004).

The consensus group agreed that such a ‘differential phase treatment’ approach is good practice in the management of schizophrenia, since it addresses the different treatment goals in various phases of the disorder and the varied needs of the patient. Regular review of treatment regimens to assess their effectiveness is also crucial, since suboptimal symptom control and unpleasant side effects may affect long-term adherence and the prognosis of the disorder. Besides, such treatment review should not be limited to clinical symptom assessment, but should also focus on other aspects including patients' quality of life, functional recovery, and

adjustment to life in the community. Lastly, further evidence-based studies in this area in the local setting are fully justified.

4. Conclusions

In Hong Kong, at least 26% of patients with schizophrenia are non-adherent to their treatment (Hui et al., 2006), and it has been reported that patients who discontinued medication are almost five times more likely to relapse than patients who continued taking medication (Kane, 2006). However, there is still a lack of genuine awareness among a significant number of local healthcare professionals regarding patients' adherence issues and the full psychosocial consequence of non-adherence. According to a local study in Hong Kong, medication management training programmes can be introduced to local community mental health practitioners to modify their understanding of the illness. In particular, avoiding persuasion, being person centred and empowering service users with choices about treatment were identified as effective approaches in managing non-adherence (Bressington et al., 2013b).

The consensus group attempted to synthesise the scientific evidence and clinical experience in Hong Kong into statements addressing the adherence issue among patients with schizophrenia. The consensus generally complies with the key principles of the National Institute for Health and Clinical Excellence (NICE) Medicines Adherence guidelines, which include providing further information and support for patients on the change of medication regimen for the effective use of their medicines, respecting patient treatment preference, and conducting regular review of treatment regimens for patients in need of adherence support (NICE CG76, 2009). It is noteworthy that the statements are considered as general clinical practice recommendations, as there are still some other areas in the adherence issue to be explored (see Table 3). For instance, although the risk factors/predictors of non-adherence are listed, the hierarchical ordering is unclear at this stage. Though a number of validated rating scales are available for assessing adherence, the applicability of these scales in the local setting should be further determined, together with individualised clinical judgement. Local clinical research should be encouraged to shed light on whether a finite or a flexible interval is more practicable, and whether the potential benefits on the use of LAI atypical antipsychotics to enhance adherence during the early course of schizophrenia are relevant in Hong Kong.

Limitations of the present consensus statements include the lack of data on the percentage increase in adherence due to treatment with atypical LAIs, the clinical benefits of using atypical LAIs in "high-risk" patients, and the direct comparison of various

atypical LAIs in terms of efficacy and safety profiles. As a result, statements 5 and 6 are partly based on expert opinions of experienced professionals in their clinical practice.

In conclusion, the above consensus statements were essentially based on the available evidenced-based data from global clinical studies and management guidelines. These statements should be monitored and updated regularly according to new findings, but they can be considered as practical clinical recommendations in the management of schizophrenia, especially for the less experienced front-line professionals.

Conflict of interest

Dr. William Tak-lam Lo is a consultant of PsyAcademy Asia Pacific, a regional medical education event organised by Janssen, since 11 March 2012.

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Table 3

Current research gaps in schizophrenia identified by the consensus group.

Topic	Research gaps in schizophrenia
Risk factors of non-adherence	Hierarchical ordering of risk factors in assessing schizophrenia is still unclear
Non-adherence rating scales	Applicability of these scales in the local setting is not determined
Definition of medication adherence	Practicability of a finite or a flexible interval over which medication adherence should be assessed is still unclear
LAI atypical antipsychotics	Their use to enhance adherence during the early course of schizophrenia or to alleviate comorbidities associated with schizophrenia is not yet clinically proven
Differential phase treatment	Effectiveness of this treatment approach is not yet clinically proven in the local setting

- randomised controlled trials and observational studies. *Br. J. Psychiatry Suppl.* 52, S20–S28.
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