Schizophrenia

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1. Introduction

Schizophrenia is a major mental disorder that imposes a significant burden on the individual including poor quality of life[1] and increased morbidity[2] and mortality;[3] it disrupts interpersonal relationships and family structures, and has significant economic costs to society.[4] While there are substantial limitations to current treatments,[5] an integrated package of biopsychosocial interventions is essential to alleviate the negative impact of the disorder and enhance quality of life.[6] Active early intervention, in particular, can improve long-term outcomes.[4]

2. Diagnosis and clinical characteristics

Schizophrenia is a heterogeneous cluster of psychotic conditions characterised by positive (delusions, hallucinations) and negative or 'deficit' (blunting of affect, avolition) symptoms, disorganised speech and behaviour, as well as mood (depressive) and cognitive impairments.

Diagnosis in terms of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*[7] requires the presence for at least 1 month (or less if successfully treated) of 2 or more of the following characteristic symptoms (in the context of the disturbance persisting for at least 6 months which includes 1 month of symptoms) (criterion A):

- Delusions
- Hallucinations
- Disorganised speech
- Grossly disorganised or catatonic behaviour
- Negative symptoms.

Further, the disorder must cause social and/or occupational dysfunction, and cannot be better accounted for by:

- Schizoaffective or mood disorders
- Substance-related disorders
- General medical conditions.

3. Assessment

3.1 Diagnostic

A detailed clinical history, mental state and careful physical examinations must inform a diagnosis made rigorously in terms of the *DSM-IV-TR,* satisfying, in particular, criterion A of the disorder.[7] Clinically indicated special investigations (bedside, serological and drug screening) should support the exclusion of other biological causes of psychosis, and screening for HIV, syphilis and psychoactive substances is recommended in the South African context. Brain imaging (computed tomography (CT) or magnetic resonance imaging (MRI)) and electro-encephalography (EEG) are recommended in first-episode patients, when the clinical picture is atypical, and when there are abnormal findings on routine examination.[4]

3.2 Pre-treatment

Clinically indicated baseline investigations prior to initiating antipsychotic treatment are directed by the clinical process and choice of initial drug therapy, and include body mass index (BMI) and waist:hip ratio (cardiovascular (CV) risk), fasting blood glucose and lipogram (metabolic risk), and full blood count and liver function tests (depending on drug selection).

A baseline electrocardiogram (ECG) is indicated before treatment if required by the product's package insert. If there is a personal history of CV disease or evidence of CV risk on physical examination, an ECG should be considered for inpatients.[6]

4. Treatment

4.1 Treatment goals

Therapeutic goals are to relieve symptoms, prevent relapse, promote recovery and improve quality of life.[6] More specifically, this includes:

- Achieving and maintain symptom alleviation
- Achieving and maintain treatment adherence
- Minimising treatment side-effects
- Monitoring physical health and drug-specific adverse event risks, e.g.
  - White cell count (WCC) (acute neutrophil count) with clozapine
  - Metabolic syndrome risk factors with olanzapine
  - Tardive dyskinesia with haloperidol
- Managing smoking and substance abuse
- Managing risk of harm to self and others.

4.2 General aspects of treatment

At the outset of management, an integrated treatment plan including pharmacological, psychological and social interventions should be formulated in terms of available resources. Pharmacological treatment remains the mainstay of therapy, while psychosocial interventions are crucial in promoting recovery and improving quality of life.[6]

While both the classification and relative efficacies of the so-called 'typical' first-generation antipsychotic (FGA) agents, such as haloperidol and chlorpromazine, and 'atypical' second-generation antipsychotic (SGA) compounds, such as risperidone and olanzapine, remain controversial, current evidence supports the following:

- Drugs from both groups are equally effective in alleviating psychosis[8]
- SGAs may have benefit in negative syndromes, and with mood and cognitive impairments[4]
- Where differences exist, the effect sizes are small to modest, except for clozapine which is more effective in treatment resistance and reducing suicide risk[4]
- SGAs, largely because of less severe extrapyramidal side-effects (EPS), are more tolerable[9]
- Each drug has a unique side-effect profile
- The choice of drug is informed by[6]
  - Access and availability
  - Shared patient-centred decision making
  - Previous experience (efficacy and side-effects), if any
  - Tailoring the side-effect profile to the individual patient
  - Choice of mode of administration (oral or parenteral)

- Recommended dosage is in the range of 300 - 1 000 mg chlorpromazine (CPZ) equivalents.[4]

Oral therapy is advised. Should parenteral therapy be considered for maintenance on the basis of patient preference or convenience or to manage non-adherence, this can be planned in the acute phase. It is logical to convert from an effective oral agent to its parenteral equivalent, and a test dose of the oral equivalent of the agent should be used before administering a long-acting injectable antipsychotic agent.

Monotherapy is recommended. There is no advantage to combining antipsychotics, which should only be done for short periods when switching agents, or in treatment-resistant settings.[4,6] Doses should not exceed 1 000 mg CPZ equivalents and/or the manufacturer's instruction as there is no additional therapeutic benefit in doing so, with added cost and side-effects.[4,6]

Loading doses or 'rapid neuroleptisation' is ill-advised as it confers no therapeutic benefit with added risks.[6] Adjunctive benzodiazepines (the evidence supports lorazepam[10]) can be used liberally to attenuate disruptive behaviour in the acute setting.[4]

Continuous dosing is advised, as intermittent or targeted dosing leads to increased risk of relapse.[4] A trial of 4 - 6 weeks is required before considering another agent.[4,6,11]

4.3 Acute pharmacological treatment

4.3.1 First episode

A recent meta-analysis[12] found no differences between FGAs and SGAs in efficacy in this population, but a clear difference in side-effect profile. In view of the vulnerability of drug-naive first-episode psychosis patients to develop EPS and tardive dyskinesia, the drug of choice is an SGA other than clozapine. Risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone and amisulpride are supported by the evidence base.[4,6,13] Dosing should start low with incremental upward titration, with the target dosage at the lower end of the therapeutic range for each agent according to the package insert.[6]

4.3.2 Multi-episode/relapse

The drug of choice will be influenced by any prior agents' efficacy and tolerability. If SGAs are available, they are generally preferred and risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone and amisulpride are supported by the evidence base.[13] Haloperidol and chlorpromazine are FGA alternatives.

4.3.3 Second-line treatment

If response to the first-line agent above is unsatisfactory, then a second trial should be considered after review of potential contributors to non-response.[6]

This second-trial agent can be another SGA or an FGA, but should be an SGA if there was a failed response to an FGA in the first trial.[4,6] Switching strategies includes cross-titration, overlap-and-taper, and abrupt change. Other than for switching to clozapine (see below), there is no evidence of difference in efficacy or tolerability.[14]

Oral monotherapy at doses not exceeding 1 000 mg CPZ equivalents and/or the manufacturer's recommendation in a continuous dosing strategy is advised for a further 4 - 6 weeks before considering the third line of treatment.[4,6,11]

4.3.4 Third-line treatment

Clozapine oral monotherapy is the next treatment of choice, at the highest tolerable dose (≤900 mg daily) for 6 months.[11] Switching requires tapering and stopping the extant agent prior to initiating clozapine, to minimise haematological risk.

Because of a non-dose-dependent risk of agranulocytosis, WCCs – absolute neutrophil counts in particular – should be monitored prior to treatment, weekly for the first 18 weeks and monthly thereafter. Considering the risk of dose-related seizures, caution and careful monitoring should be exercised at doses above 450 mg daily.[15]

4.4 Long-term maintenance

Half of all patients stopping medication will relapse within 6 - 10 months, compared to one-fifth on treatment.[6] Long-term antipsychotic treatment reduces the risk of relapse over several years by two-thirds.[16]

Continuation of pharmacological treatment that was effective in the acute and stabilisation phases is advised. While many practitioners attempt dose reduction during maintenance, the evidence suggests that even gradually decreasing doses increases the risk of relapse.[17] Continuous dosing is advised as intermittent or targeted dosing leads to increased risk of relapse.[4]

Oral therapy is usual, but long-acting intramuscular preparations should be considered for maintenance on the basis of patient preference or convenience, or to manage non-adherence.

The minimum duration of treatment for first-episode patients is 1 year symptom-free if the episode is of mild severity and responds well to treatment, and 2 years symptom-free in severe cases or those slow to respond initially.[17] Second-episode patients require at least 2 and up to 5 years symptom-free before drug withdrawal can be considered. Indefinite treatment is advised after a third episode.[17]

4.5 Non-pharmacological treatment

4.5.1 Psychological interventions

These are focused on the individual (cognitive behaviour therapy, psycho-education, supportive psychotherapy) and the family (psycho-education, family therapy). These can be introduced during the acute phase of illness, but are more usually commenced in the stabilisation period.[6]

4.5.2 Social interventions

Long-term goals of treatment adherence and symptom reduction, limitation of injurious behaviours (smoking, substance abuse, suicide risk) and improved quality of life are supported by social interventions, including assertive community programmes, social skills training, appropriate housing, supported employment and adaptation to life in the community. These may be required during the acute phase of illness, but are more usually commenced in the stabilisation period.[6]

4.6 Special populations

4.6.1 First-episode psychosis

In view of the vulnerability of drug-naïve first-episode psychosis patients to develop EPS and tardive dyskinesia, the drug of choice is an SGA other than clozapine. Dosing should start low with incremental upward titration, with the target dosage at the lower

end of the therapeutic range of each agent according to package insert.[6] Oral therapy is recommended.

4.6.2 Electro-convulsive therapy (ECT)

While ECT is considered a last-line treatment[4] in uncomplicated schizophrenia, it has a role in early acute treatment in the context of extreme psychomotor agitation, catatonia, pregnancy, or when life is at risk.

4.7 Managing partial and non-responders

4.7.1 Non/partial response

If response to any line of treatment is unsatisfactory, then a further line of intervention should be considered after review of potential contributors to non-response.[6] This includes:

- Review of the diagnosis
- Review of treatment adherence
  - Drug choice
  - Dosage
  - Duration
- Adequacy of psychosocial interventions
- Presence of comorbid:
  - Substance abuse
  - Psychiatric illness
  - Physical illness
  - Pharmacotherapy.

4.7.2 Treatment resistance

While there are many definitions of treatment-resistant schizophrenia, for the purposes of this guideline it is taken to mean 'insufficient improvement in target symptoms despite treatment at the recommended dosage for at least 6 weeks with at least 2 antipsychotic agents, one of which was an SGA other than clozapine'.[4]

In addition to a review of potential contributors to non-response as above,[6] a multidimensional assessment of positive, negative, affective and cognitive symptoms, as well as social and vocational function and quality of life, is indicated.[4]

With ongoing insufficient response to maximum dose clozapine, the options (for which there is only limited evidence) are:

- Combining clozapine with another SGA that does not compound its side-effects
- Augmentation with mood stabilisers
  - Lamotrigine has some evidence for utility[4]
  - Valproate when hostility is a problem[18]
  - Lithium when depression is troublesome[19]
- Benzodiazepines can be added in cases of agitation, for short-term use
- ECT is a last-line treatment.[4]

Fig. 1 outlines the treatment algorithm.

5. Summary points

- Both typical FGA agents and atypical SGA agents are effective in schizophrenia. Any differences in efficacy between these agents are small to modest. There are, however, clear differences in side-effect profiles.
- Monotherapy is recommended as there is no advantage to combining antipsychotics.
- A loading dose ('rapid neuroleptisation') is ill-advised, as it confers no therapeutic benefit with added risks.
- Risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone and amisulpride are effective in first-episode psychosis patients.
- For multi-episode patients, consider risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone and amisulpride. Haloperidol and chlorpromazine may be considered as alternatives to FGAs.
- A trial of 4 - 6 weeks is required before considering an alternative agent.
- A second trial agent may be another SGA or an FGA, but should be an SGA if

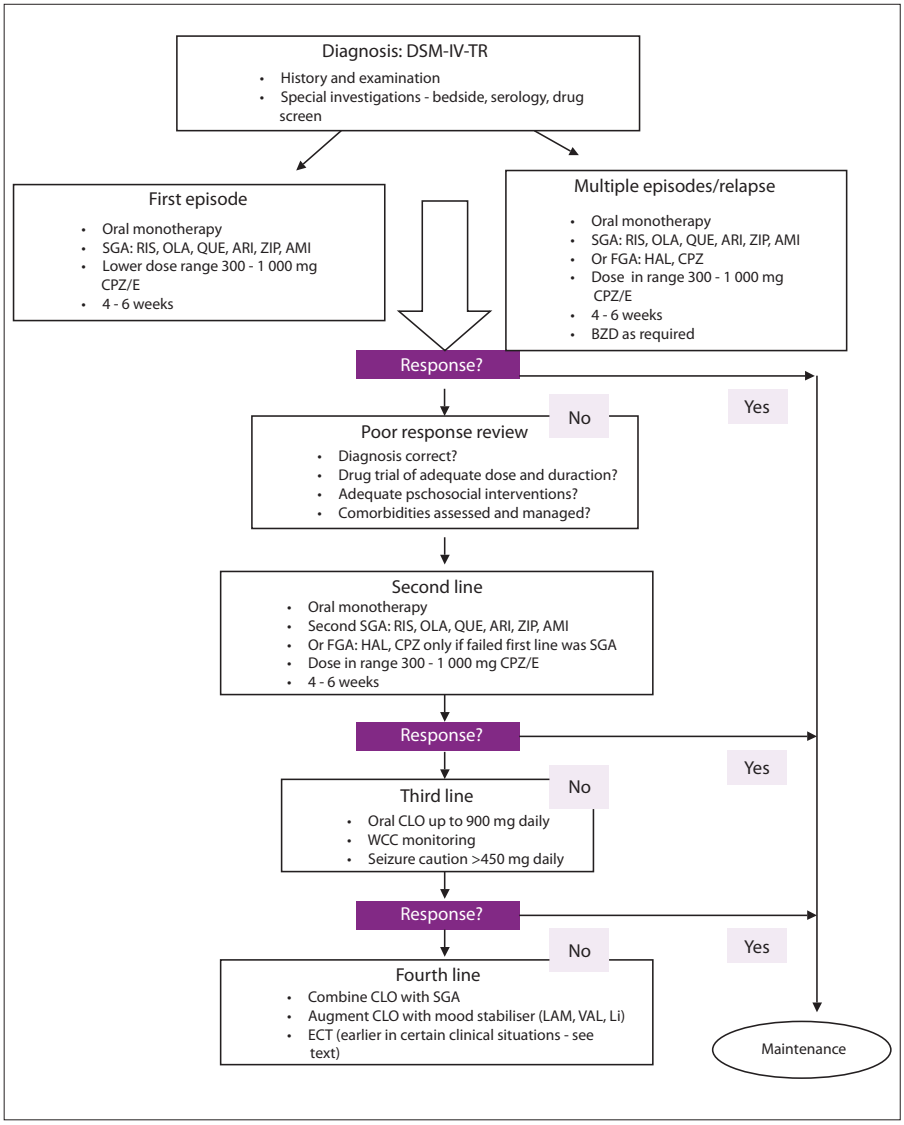

Fig. 1. Treatment algorithm. FGA = first-generation antipsychotic; HPL = haloperidol; CPZ = chlorpromazine; CPZ/E = chlorpromazine equivalents; SGA = second-generation antipsychotics; RIS = risperidone; OLA = olanzapine; QUE = quetiapine; ARI = aripiprazole; AMI = amisulpride; CLO = clozapine; BZP = benzodiazepines; LAM = lamotrigine; VAL = valproate; Li = lithium.

there was a failed response to an FGA in the first trial. Third-line treatment is clozapine.

- Clozapine is more effective than other FGA and SGA agents in treatment resistance and reduction of suicide risk.
- If there is an insufficient response to a maximum dose clozapine, consider combining clozapine with another SGA, or augmenting with a mood stabiliser, ECT, or adding a benzodiazepine in the short-term to control agitation or disruptive behaviour.
- Half of all patients stopping medication will relapse within 6 - 10 months, compared to one-fifth on treatment.
- Minimum treatment duration for first episode patients is 1 year symptom-free if the episode is of mild severity and responds well to treatment, and 2 years symptom-free in severe cases or those slow to respond initially.
- Second-episode patients require at least 2 - 5 years of medication while symptom-free before discontinuation is considered, while patients who have had 3 or more episodes should be treated indefinitely.

References

1. Jones PB, Barnes TRE, Davies L, et al. Randomised control trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost utility of the latest antipsychotic drugs in schizophrenia study (CUtLASS 1). Arch Gen Psychiatry 2006;63:1079-1086. [http://dx.doi.org/10.1001/archpsyc.63.10.1079]
2. Murray CJ, Lopez AD. Global mortality, disability and the contribution of risk factors: Global burden of disease study. Lancet 1997;349:1436-1442. [http://dx.doi.org/10.1016/S0140-6736(96)07495-8]
3. Brown S, Inskip H, Barraclough B. Causes of excess mortality of schizophrenia. Br J Psychiatry 2000;177:212-217. [http://dx.doi.org/10.1192/bjp.177.3.212]
4. Falkai P, Wobrock T, Lieberman J, et al. World Federation of Societies of Biological Psychiatry (WFSBP). Guidelines for biological treatment of schizophrenia, Part 1: acute treatment of schizophrenia. World Journal of Biological Psychiatry 2005;6:132-191. [http://dx.doi.org/10.1080/15622970510030090]
5. Lieberman JA, Scott Stroup T, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209-1223. [http://dx.doi.org/10.1056/NEJMoa051688]
6. National Institute for Health and Clinical Excellence (NICE). Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. London: NICE, 2009: Clinical Guidance 82. (http://www.nice.org.uk/guidance/index.isp?action=bvID&o=11786)
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association, 2000.
8. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: A meta-analysis. Lancet 2009;373:31-41. [http://dx.doi.org/10.1016/S0140-6736(08)61764-X]
9. Fleischhacker WW. Second generation antipsychotics. Psychopharmacology 2002;162:90-91. [http://dx.doi.org/10.1007/s00213-002-1064-8]
10. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia, 2nd edition. Am J Psychiatry 2004;161:1-114.
11. Kenneth O, Jobson MD. The International Psychopharmacology Algorithm Project (IPAP) - Schizophrenia Algorithm, Schizophrenia Algorithm nodes. 2006. http://www.ipap.org/ (accessed July 2013).
12. Crossley NA, Constante M, MacGuire P, et al. Efficacy of atypical v. typical antipsychotics in the treatment of early psychosis: Meta-analysis. Br J Psychiatry 2010;196:434-439. [http://dx.doi.org/10.1192/bjp.bp.109.066217]
13. Leucht S, Komossa K, Rummel-Kluge C, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry 2009;166:152-163. [http://dx.doi.org/10.1176/appi.ajp.2008.08030368]
14. Kane JM, Leucht S, Carpenter D, et al. The Expert Consensus Guideline Series: Optimising pharmacologic treatment of psychotic disorders. J Clin Psychiatry 2003;64:1-100.
15. Gibbon CJ, Blockman M. South African Medicines Formulary, 8th ed. Cape Town: Health and Medical Publishing Group, South African Medical Association, 2008.
16. Kissling W. Guidelines for neuroleptic relapse prevention in schizophrenia. 1991. Berlin: Springer, 1991.
17. Falkai P, Wobrock T, Lieberman J, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, Part 2: Long-term treatment of schizophrenia. World Journal of Biological Psychiatry 2006;7:5-40. [http://dx.doi.org/10.1080/15622970500483177]
18. Citrome L, Casey DE, Daniel DG, et al. Adjunctive divalproex and hostility among patients with schizophrenia receiving olanzapine or risperidone. Psychiatr Serv 2004;55:290-294. [http://dx.doi.org/10.1176/appi.ps.55.3.290]
19. Leucht S, Kissling W, McGrath J. Lithium for schizophrenia revisited: A systematic review and meta-analysis of randomized controlled trials. J Clin Psychiatry 2004;65:177-186. [http://dx.doi.org/10.4088/JCP.v65n0206]