Lynn Haygarth Senior Lecturer in Pharmacy Practice, University of Huddersfield
Steve Hemingway, Senior Lecturer in Mental Health
Practical Prescribing in schizophrenia

Abstract

This paper presents a major overview for the non medical prescriber when considering prescribing an antipsychotic to have the optimum outcome.

Key messages

- Antipsychotics continue to be the cornerstone of therapy for the treatment of schizophrenia.
- Outcomes depend on adherence with therapy.
- Patient choice in therapy is as important as clinician choice.
- There is no one drug fits all.
- Second generation/atypicals are as effective as first generation/typical antipsychotics but not superior and can cause side effects with long term problems
- The involvement of the patient in the treatment plan is necessary including initial and ongoing physical health monitoring
- The drug costs are less than 5% of the burden of costs in the care of schizophrenia

Introduction

The most common intervention for the treatment of schizophrenia is the prescribing of antipsychotics. There is much discussion about the most suitable antipsychotic to choose, a first generation (typical) antipsychotic or a second generation (atypical) antipsychotic. The evidence does not suggest there is much difference in efficacy between antipsychotics but there are substantial differences in side effect profile (NICE 2014). The antipsychotic that is the exception is clozapine when there is significant evidence of efficacy over other antipsychotics and in particular a reduction in the risk of suicide (Meltzer et al 2003). First generation antipsychotics (FGAs) traditionally cause more movement disorders known as extra pyramidal side effects (EPSEs) and second generation antipsychotics (SGAs) are more likely to cause endocrine side effects in particular weight gain and links to diabetes. However individual antipsychotics have their own individual side effect profiles and it is an important role of the prescriber to understand the pharmacology of the individual antipsychotics including the most appropriate formulation for individual patients.

This article will firstly, discuss the dopamine hypothesis is as a background to prescribing antipsychotics. Then, secondly issues in the choice of antipsychotic are discussed. Thirdly, prescribing considerations for first and second generation antipsychotics with an emphasis on side effect profiles are outlined. In conclusion the need to individualise the prescribing decision so that the patient is involved in the prescribing decisions about medication for them are made.

Dopamine hypothesis

The dopamine hypothesis of schizophrenia suggests that at least the positive symptoms of schizophrenia are due to hyperactivity of dopamine in the mesolimbic pathway in the brain. Antipsychotics block dopamine resulting in reduction in the positive symptoms e.g. hallucinations, delusions, aggression. Side effects that commonly occur can be due to blocking dopamine pathways in other areas of the brain. In particular blocking dopamine in the nigostriatal pathway results in movement disorders known as

extrapyramidal side effects (EPSEs). Potent D2 blockers e.g. haloperidol are most likely to cause these. Although the majority of clinical trials used haloperidol as a comparator it is not currently as widely prescribed as the SGAs. Blocking dopamine in the tuberoinfundibular pathway can result in increased prolactin release potentially resulting in breast enlargement and lactation. Sulpiride and risperidone have a particular side effect of raised prolactin. Other side effects can be due to the lack of specificity for dopamine receptors with other alpha adrenoreceptor and histamine receptor activity causing postural hypotension and sedation and antimuscarinic activity causing dry mouth, blurred vision and constipation.

Table 1 Considerations for choice of drug

- *Patient Choice*
- *Diagnosis*
- *Licensed use within product licence and BNF limits*
- *Prescribing Guidance*
  - *NICE*
  - *Local –Trust or Area Prescribing Committee*
  - *Formulary*
- *Cost*
- *Advance Directives*
- *Informed patient consent /Concordance with the chosen regimen*
- *Previous response*
- *Side effects*
- *Co-morbid psychiatric or medical condition*
  - *Drug-drug interactions*
  - *Ability to swallow oral formulations*
- *Concurrent drug therapy*
- *Metabolic changes associated with age, gender, ethnicity*
  - *Lower doses in older people*
- *Physical health*
  - *Cardiovascular status*
  - *Smoker*
  - *Diabetes*
  - *Ability to swallow tablets*
  - *Lifestyle*
  - *Weight*
- *Allergies and Sensitivities*
- *Metabolic changes associated with age, gender, ethnicity*
  - *E.g Lower doses in older people*
- *Medicines prescribed ie consider drug-drug interactions*

Choice

The best choice of antipsychotic is the one the patient is comfortable to take and is most likely to adhere to in the longer term. There is a plethora of evidence based guidance available to support prescribers from NICE guidance to local prescribing formularies. There has been a lot of emphasis on the cost of individual antipsychotics, however safety and adherence have a very important part to play as it is shown that antipsychotic drug costs are less than 5% of the total burden of cost of schizophrenia (Lieberman et al, 2005, Jones et al 2006). The CATIE study from the USA showed them to be 2.1% and the CUTLASS study from the UK to be 3.8% of the overall cost of treatment.

Medicine based evidence

Much of the evidence has been developed by comparing haloperidol to the second generation antipsychotics risperidone, olanzapine, quetiapine and aripiprazole as they were developed for market (Healy, 2016).Two important studies that have informed choice and outcome from prescribing are the CATIE (USA) and CUTLASS (UK). In the CATIE study in the United States the comparator first generation antipsychotic was perphenazine, which, although available in the UK is not widely prescribed (Lieberman et al). A cohort study of primary care patients carried out between 2007 and 2011 (ref) showed the second generation antipsychotics to be more commonly prescribed for schizophrenia with the most common in primary care being risperidone, quetiapine and olanzapine. Aripiprazole has only more recently become available as a generic and asenapine and lurasidone being more recently introduced there is less data available from primary care. The prescribing of the FGAs, chlorpromazine, haloperidol and trifluoperazine reduced over the period of the study. In addition clozapine is normally prescribed in secondary care. Although NICE guidance recommends that both first and second generation antipsychotics should be considered first line it is clear that the majority of prescribing for schizophrenia falls to second generation antipsychotics with the use of typical antipsychotics for schizophrenia falling. In trials olanzapine caused most weight gain and dyslipidaemia, quetiapine caused most anticholinergic effects and risperidone caused the most hyperprolactinaemia and sexual side-effects compare to other SGAs. Perphenazine had highest rates of discontinuation for extrapyramidal side-effects, even though direct measures of these effects did not differ significantly between drugs.

Choice and other variables in prescribing

It is common to focus on the evidence base when prescribing however this requires to be backed up by the pharmacology of the drug, the physiological condition of the patient and the licensed indications for the individual antipsychotic. Evidence suggests that it is the length of treatment and adherence with the prescribed regimen that most improves patient outcome. It is also necessary to consider the licensed indications for the product particularly for use in adolescents and older people. This information is readily available from the most up to date British National Formulary (BNF) and the summary of product characteristics (SPC), available from the electronic Medicines Compendium (eMC) at ww.medicines.org.uk, of the individual drugs (BNF 2016).

The recent article on prescribing for schizophrenia in pregnancy (Hardy 2017) gave a full account of the individual drugs so it is not necessary to repeat this information here. A particularly useful reference source to support both clinician and patient choice is the “Choice and medication website” where there is information to support choice of one antipsychotic over another for both the prescriber and the patient. This is can be accessed via the http://www.choiceandmedication.org/swyp/.*
Prior to initial prescribing and ongoing throughout the treatment period physical health monitoring is essential and pre-screening is helpful wherever possible (NICE, 2014). In particular for haloperidol an ECG is recommended prior to treatment. It may not always be possible to get this completed prior to starting treatment however it is important to continue to consider getting this test with reference to the mental state of the patient.

It is important to consider the formulation of the antipsychotic when prescribing and to understand the pharmacokinetics of the antipsychotic and formulation being prescribed. Oral formulations are the most common with depot antipsychotics only being chosen normally there are adherence issues and if it convenient for the patient (Edward & Alderman, 2013).

Prescribing considerations: First generation antipsychotics

Chlorpromazine was the first antipsychotic to be widely prescribed but is no longer a treatment of choice for schizophrenia. It is used in doses of 75mg to 300mg daily with dose titration being important. It is a low potency antipsychotic, as well as blocking dopamine it affects muscarinic, histaminic and alpha -adrenoceptors and may cause sedation, hypotension and constipation. There is a risk of neutropenia, prolongation of the QT interval, increased susceptibility to sunburn, impairment of body temperature, retinal pigmentation all leading to reduction in prescribing.
Haloperidol is a potent dopamine D2 blocker causing a high incidence of EPSEs. It is prescribed in doses of 2mg to 10mg per day ideally using dose titration with the lowest possible dose.
Trifluoperazine is a potent D2 blocker used in doses of 5mg twice daily (increased if required). It causes EPSEs in particular dystonic reactions.
Extra pyramidal side effects may be caused by blocking dopamine in the nigrostriatal pathway the brain. These can affect the patient in different ways in particular dystonia causing severe muscle stiffness and oculogyric crisis. This can be extremely distressing and it is important to understand that patients suffering from this are unlikely to be adherent to treatment regimens in the future. In the past these were usually identified by clinicians however there is now a generation of clinicians working in mental health who have not seen these side effects since the reduction in prescribing. These are well described in the BNF and include
Akathisia a feeling of inner restlessness which is very difficult to treat other than by changing the antipsychotic or redcing the dose
Dystonia -Muscle spasms and oculargyric crisis which may be inceased in young males. This can be treated by using an antimucarinic e.g. procyclidie
Drug induced Parkinsonism - tremor, slowing up which may be higher in elderly females. This can be treated by using an antimucarinic e.g. procyclidine
Tardive Dyskinesia -lip smacking, tongue protrusion, pill rolling coming on in often after many years and it can be permanent. Gradual reduction of treatment and antimuscarinics is important.
Neuroleptic Malignant Syndrome less than 1% -fever, rigidity, tachycardia, unstable BP, fluctuating consciousness. There can be very high creatinine phosphokinase (CPK) levels and altered liver function tests (LFTs). Treatment requires stopping all antipsychotics.

Anticholinergics (antimuscarinics) can be used to moderate the effects of EPSEs in particular dystonia and Parkinson's type side effects. These are not likely to be effective for akathisia and may worsen tardive dyskinesia. Other strategies include lowering the dose or switching to an SGA
Examples include

- Trihexylphenidyl (Benzhexol)
- Orphenadrine
- Procyclidine

- Can antagonise effects of antipsychotics
- Side effects include
  - Dry mouth, blurred vision, constipation

Prescribing considerations: Second generation antipsychotics (SGAs)

Amisulpride is prescribed for schizophrenia with predominantly positive symptoms at doses between 400 and 800mg daily. It is normally administered twice daily. It has a low incidence of cardiotoxicity, sedation, EPSE's & weight gain but a high incidence of prolactin elevation. It is available in generic form.

Aripiprazole is prescribed as a once daily dose of 10mg to 20mg per day with a 5mg starting dose for older people. The licensed dose is up to 30mg per day but this is not routinely recommended due to lack of evidence of benefit. It has a low incidence of, weight gain, EPSE's, cardiotoxicity & hyperprolactinaemia. Aripiprazole is the only atypical antipsychotic with partial agonistic activity at dopamine receptors. When dopamine levels are diminished, the partial agonistic activity of aripiprazole increases dopamine transmission due to a lower degree of occupation of dopaminergic receptors by dopamine.

Risperidone is well tolerated at less than 6mg/day in adults, 4mg/day in older people. It has a low incidence of cardiotoxicity & EPSE's. It may cause mild hypotension, mild weight gain & raised prolactin. It is available in an oro-dispersible preparation and a generic form. It is also available as a depot preparation which can be administered at fortnightly dose intervals.

Olanzapine is prescribed at a dose of 10 to 20mg for schizophrenia. Starting doses are lower in older people. It has a low incidence of cardiotoxicity, EPSE's & prolactin elevation. It may cause hyperglycaemia, moderate sedation & weight gain. It is available as an oro-dispersible preparation and in a generic form. It is also available as a depot preparation although there are strict post dose administration monitoring requirements which have reduced the usefulness of this preparation.

Quetiapine is prescribed at doses of between 150mg to 750mg daily with twice daily dosing for the standard preparation and once daily dosing for the extended release preparation. Dose titration is important and should be carried out as per the SPC. There are generic forms available but no depot. It has a low incidence of EPSE's, cardiotoxicity & hyperprolactinaemia.

Clozapine is the only antipsychotic drug recommended for treatment resistant schizophrenia and is licensed for use after an adequate trial of two antipsychotics of which one should be an SGA. There is evidence that clozapine can potentially reduce the risk of suicide. Its complex licensing arrangements make it more difficult to prescribe than other antipsychotics and as a result there is no depot preparation available. Dose titration is important with risks of hypotension and tachycardia if the doses are increased rapidly. Common dose regimens are between 300mg and 600mg daily. There is a risk of neutropenia and full blood counts (FBC) are required weekly for 18 weeks of treatment, 2 weekly until one year, monthly thereafter while treatment continues. Side effects include sedation hypersalivation seizures weight gain cardiomyopathy and constipation. It is contraindicated for use with depots antipsychotics, carbamazepine and any medicines that may lower white cell count. Potential drug interactions can be identified due to the effect on cytochrome P450 of enzyme inducers. A particular problem that always needs considering is the effect of tobacco smoke on clozapine levels. Stopping smoking can result in the raising of the clozapine level leading to increased side effects.

Weight gain is a particular problem with SGAs. Clozapine and olanzapine are the highest risk, quetiapine and risperidone are moderate risk with aripiprazole and amisulpride the lowest risk. A study by Bobes et al 2003 showed that olanzapine and risperidone were risk factors for weight gain over haloperidol.

Physical health monitoring is required throughout the course of treatment and this together with involving the patient in the treatment is the key intervention recommended in the NICE clinical guideline for psychosis and schizophrenia. (NICE 2016)

Depot antipsychotics Do we need to include FGA depots and SGA depots in each section??
Depot antipsychotics were developed to support adherence with treatment. Full information on dosing, prescribing and administration of depot antipsychotics can be found in the document long acting intramuscular injections 5th edition https://hydra.hull.ac.uk/resources/hull:13659 (Feetam et al 2016). Prescribers should be aware of the pharmacokinetics of the depot antipsychotic being prescribed. There is no advantage to weekly injections although these are commonly prescribed in clinical practice. Information on the pharmacokinetics of depot antipsychotics can be found in the Psychotropic drug directory (Bazire 2016). The availability of both first generation and second generation depot has been shown to be important no long acting injection being clinically superior to another in a trial comparing the effectiveness of flupenthixol, risperidone, and zulclopenthixol in clinical practice (Shajahn et al 2010). There is emerging evidence that clozapine and depot antipsychotics have the highest rates of prevention of relapse in schizophrenia and reduced rates of re-hospitalization over other oral antipsychotics. This was evidenced in a nationwide study in Sweden of 29,823 patients run between 2006 and 2013 (Tihonen et al 2016).

Table 1

First Generation Antipsychotics oral		
Chlorpromazine	75mg - 300mg daily in divided doses	No longer commonly prescribed
Haloperidol	2 -10mg	Potent D2 blocker may cause EPSEs
Sulpiride		Risk of hyperprolactinaemia
Trifluoperazine		
First generation depots		
Flupentixol decanoate	50mg every 4weeks to 300mg every 2 weeks	Test dose of 20mg recommended
Fluphenazine decanoate	12.5mg (6.25mg	Test dose of 12.5mg (6.25mg in elderly)

	elderly) – 100mg every 2-5weeks	recommended
Haloperidol decanoate	50 mg - 300mg every 4 weeks	Test dose of 25mg recommended
Zuclopentixol decanoate	200mg - 5oomg every 1-4weeks	Test dose of 100mg recommended

Second Generation antipsychotics oral		Common side effects
Amisulpride		
Aripiprazole		
Clozapine		
Olanzapine		Weight gain, dyslipidaemia
Quetiapine		Antimuscarinic effects
Risperidone		
Second generation depots		
Aripiprazole	400mg monthly	Treat with oral aripiprazole prior to injection
Olanzapine pamoate monohydrate	150mg-300mg every 4 weeks	Treat with oral olanzapine prior to injection
Paliperidone palmitate	75mg -150mg monthly after dose titration	150mg day 1, 100mg day 8 then 75-150mg a month later
Risperidone	25mg to 50mg every two weeks	Treat with oral risperidone prior to injection. Continue for

Conclusion

This article has provided a practical background to prescribing antipsychotics. Antipsychotics can help the patients to live a meaningful and settled life when they experience the symptoms of psychosis and/or schizophrenia. However as shown in article the balance between the benefits and risks of prescribing antipsychotics need to be considered by the prescriber so that the optimisation of medicine is the outcome. Therefore the minimisation of side effects with the lowest dose of antipsychotic to treat symptoms needs to be at the foremost of the prescriber's decision making. Finally involving patients in the prescribing decisions that are made about them is paramount. The best way to involve and get the best possible outcome is that patients are informed and agree with the prescription as appropriate to their lifestyle and health needs. This may be difficult when there are capacity issues but should still be at the forefront of all communication with the person who is prescribed antipsychotics.

Further information is available in the handy chart for psychosis from the choice and medication website Always use the most up to date BNF and SPC when prescribing.

**Choice and medication website is available by subscription via a link to the local mental health services website. The whole of Great Britain subscribe except Sheffield, South London and Maudsley (SLAM), Oxleas, Mersey Care and Lancashire Care who will have their own information sources.*

References

Barnes T and the Schizophrenia Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for the treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology. (2010).

Bazire S. Psychotropic drug directory (2106)

Bobes J, Rejas J, Garcia-Garcia R, Rico-Villademoros F, Garcia-Portillo M, Fernandez I, Hernandez GWeight gain in patients with schizophrenia treated with risperidone, olanzapine, quetiapine or haloperidol: results of the EIRE study. Schizophrenia Research. Volume 62 Issues1-2 2003 77-78

Emsley R, Oosthuize P. Evidence-based pharmacotherapy of schizophrenia. Cambridge University Press. 2005.

Feetam C &White J Eds. Guidance on the administration to adults of oil based depot and other long acting intramuscular antipsychotic injections. 5th edition 2016

Hardy S, Prescribing for schizophrenia and psychosis in pregnancy Nurse Prescribing Volume 15 2 2017

Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, Murray RM, Markwick A, Lewis SW. Randomized controlled trial of 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– 87.

Kane J, Honigfeld G, Singer J Meltzer Clozapine for the treatment resistant schizophrenic. A double blind study with chlorpromazine Arch Gen Psychiatry 1988;45 (9):789-796

Lewis SW, Barnes TRE, Davies L, Murray RM, Dunn G, Hayhurst KP, Markwick A, Lloyd H, Jones PB. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull 2006 ; 32: 715– 23.

Lieberman JA1, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia.
N Engl J Med. 2005 Sep 22;353 (12):1209-23. Epub 2005 Sep 19.

McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, Swartz MS, Perkins DO, Keefe RSE, Davis CE, Severe J, Hsiao JK, for the CATIE Investigators. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 2006; 163: 600– 10.

Nasrallah H. 2003. A review of the effect of atypical antipsychotics on weight. Psychoneuroendocrinology, 28 (suppl.1), 83-96.

National Institute for health and care excellence (2014) Psychosis and and schizophrenia in adults:prevention and management CG178 2014

Rocio Perez-Iglesias, Benedicto Crespo-Facorro, Obdulia Martinez-Garcia, Maria L. Ramirez-Bonilla, Mario Alvarez-Jimenez, Jose M. Pelayo-Teran, Maria T. Garcia-Unzueta, Jose A. Amado, Jose L. Vazquez-Barquero Weight gain induced by haloperidol, risperidone and olanzapine after 1 year: Findings of a randomized clinical trial in a drug-naïve population
Schizophrenia Research, Volume 99, Issues 1–3, 2008, pp. 13-22

Shajahan P, Spence E, Taylor M, Darlington D, Pelosi A. Comparison of effectiveness of depots antipsychotics in routine clinical practice. The Psychiatrist, 2010 34,273-279

Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtälä J, Hoti F, Jedenius E, Enkusson D, Leval E, Sermon J, Tanskanen A, Taipale H, Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29 823 Patients With Schizophrenia JAMA Psychiatry. 2017 Jul 1;74(7):686-693

Abilify Maintena SPC http://www.medicines.org.uk/emc/medicine/31386 (accessed 12/08/17)
Modecate SPC https://www.medicines.org.uk/emc/medicine/6956 (accessed 12/08/17)
Modecate conc SPC http://www.medicines.org.uk/emc/medicine/6955 accessed 12/08/17)
Trevicta SPChttps://www.medicines.org.uk/emc/medicine/32050 (accessed 12/08/2017).