Antipsychotic medicines are the mainstay for managing psychosis in patients with schizophrenia, bipolar and other psychotic presentations but this class of medicines have other properties; these have resulted in their use for a number of other presentations as well as being associated with significant adverse reactions. Although the distinction is not clearly defined they are primarily classified as typical and atypical antipsychotics.

Typical antipsychotics:

- The typical classification is associated with older antipsychotic developed in the 1950-60s. This group is noted as having a higher incidence of Parkinson-like side effects and long term use (5-10 years) causing tardive dyskinesia, a disabling neurological disorder, in a significant proportion of patients. The older typical antipsychotics are predominantly dopamine blockers, but have a mix of properties but are best considered in terms of their potency and adverse effect profile:
  - **Low potency** medicines have a broad mix of adverse effects including sedation, weight gain, postural hypotension, anticholinergic side effects, as well as Parkinson-like tremor and motor restlessness (akathisia); they include chlorpromazine, methotrimeprazine, and thioridazine (now withdrawn due to the high risk of QT prolongation)
  - **Intermediate potency** agents are associated with less sedation but more marked Parkinson-like side effects especially akathisia and included thiothixane, perphenazine, pericyazine, trifluoperazine and zuclopenthixol
  - **High potency** agents include haloperidol, pimozide and fluphenazine. Parkinson-like side effects are significant. These medicines have fewer effects on noradrenaline, histamine and acetylcholine pathways so have a lower incidence of sedation, weight gain and anticholinergic side effects

- In psychiatry the typical antipsychotics have been largely replaced for the treatment of schizophrenia, bipolar disorder and other psychiatric presentations by newer atypical medicines. Typical antipsychotics still have a limited role for a number of conditions as off-licence indications.
  - **Palliative Care**: haloperidol/methotrimerperazine are useful as second line agents in palliative care in pain control pumps as adjuncts for the management of nausea or terminal near-death restlessness
  - **Delirium**: haloperidol has been used at low doses (0.5-1mg qid) to manage delirium in a hospital setting
  - **Intractable hiccups**: chlorpromazine is a second/third line agent for intractable hiccups associated with palliative care. although caution is required as the agent can cause significant postural hypotension
  - **Agitation/anxiety**: chlorpromazine, haloperidol, methotrimeprazine, trifluoperazine and zuclopentixol have been used at low doses to reduce arousal in agitated patients with personality disorders or severe anxiety, but the Parkinson-like side effects and the newer atypical agents (especially quetiapine) have replaced typical agents for this indication
Atypical antipsychotics

- Atypical antipsychotics have mixed dopaminergic and serotonergic action. They have different properties on dopamine pathways so have a far lower burden of Parkinson-like side effects, though the emergence of metabolic side effects including marked weight gain, dyslipidaemia and glucose impairment has become problematic for a number of this group.
  - **Risperidone**: is the atypical medicine with the highest potency for dopamine receptors; noradrenergic activity can result in postural hypotension when initiated, so gradual dose increase is recommended. Risperidone has potent antipsychotic properties, without undue sedation, which makes this antipsychotic useful in patients with psychosis with a more paranoid presentation, where behavioural disturbances or mood fluctuations are less prominent. The long acting injectable formulation has advantages in patients with reduced oral adherence. At doses of 6mg daily or above patients may experience Parkinson-like adverse effects, including tremor, dyskinesia, rigidity and akathisia, raised prolactin can occur and result in amenorrhea and sexual dysfunction, weight gain and metabolic syndrome has resulted in type II diabetes in some patients, elderly patients taking risperidone have an increased incidence of stroke.
  - **Olanzapine**: has effects on more neuroreceptors compared with risperidone and is associated with more sedative properties and a higher incidence of weight gain, as well as being a potent antipsychotic. Parkinson-like side effects are low but akathisia has been observed. Olanzapine has good efficacy as a mood stabiliser in patients with schizoaffective or bipolar presentations. The weight gain properties associated with olanzapine are significant and patients need to be monitored closely for risk of glucose impairment and type II diabetes. Despite these concerns olanzapine has better patient acceptability compared with other antipsychotics due to its ability to reduce anxiety associated with psychosis.
  - **Quetiapine**: is less potent and has a lower association with Parkinson-like side effects. The lower potency of quetiapine is matched with reduced efficacy in treating psychosis in patients with more severe schizophrenia. Quetiapine has found a role at lower doses (25mg-300mg per day) for managing agitation and heightened arousal in patients with anxiety disorders, depression and psychosis secondary to dementia and in patients with personality disorders. Quetiapine has been considered useful when practitioners are wishing to avoid prescribing benzodiazepines for these indications. Although quetiapine lacks the potential for dependence associated with benzodiazepines, the agent is best considered as a short term adjuvant to manage distress as it has adverse effects in its own right. Quetiapine adverse effects include increased risk of stroke in the elderly, weight gain and risk of metabolic syndrome and type II diabetes which has been documented in some patients on low doses (50mg-100mg a day) and in the elderly postural hypotension.
  - **Clozapine**: is the antipsychotic with greatest efficacy for treating schizophrenia but it is association with significant adverse reactions is reserved for patients with schizophrenia who have not responded to effective
doses of other antipsychotics, have experienced significant adverse effects or are incapacitated by negative symptoms. The incidence of Parkinson-like side effects with clozapine is minimal. Side effects include tachycardia, postural hypotension, night time drooling, metabolic syndrome and incontinence of urine in some patients. More severe clozapine adverse events include:

- **Neutropenia.** Clozapine is associated with a high incidence of blood dyscrasias including neutropenia and agranulocytosis, so patients require on-going full blood counts which are weekly for the first 18 weeks of treatment then monthly (unless low neutrophils/white blood cells require more frequent monitoring usually weekly testing) and the medicine must be discontinued if neutrophils drop below $1.5 \times 10^9$ or white blood cells drop below $3 \times 10^9$. Patients whose bloods show a rapidly dropping neutrophil/white blood cell count (over three tests) may also need to stop clozapine or be closely monitored.

- **Myocarditis.** Clozapine has also been associated with myocarditis, which can present in the first 4-12 weeks or treatment and less frequently at any point latter in treatment. Symptoms are non-specific and can include tachycardia, fluctuating blood pressure, flu-like symptoms and shortness of breath. Laboratory finding may show a raised troponin.

- **Severe constipation.** There have been cases of death within New Zealand were clozapine in association with other constipating medicines (anti-cholinergic medicines, opiates, calcium channel blockers) has caused ischemic bowel.

- **Amisulpride:** amisulpride has atypical properties at lower doses (<300mg), and at higher doses has more typical antipsychotic activity, it preferably blocks limbic rather than striatal pathways. It has some benefits in terms of having a lower risk of metabolic syndrome, postural hypotension and anticholinergic adverse effects, although it can cause a marked increase in prolactin with associated risk of galactorrhoea, amenorrhoea, gynaecomastia, breast pain, and erectile dysfunction. Weight gain is common. Amisulpride has been used with clozapine in patients with severe refactory schizophrenia to augment antipsychotic treatment.

- **Aripiprazole:** aripiprazole has partial agonist properties on dopamine pathways so differs from other atypical agents. It has low Parkinson-like adverse effects, metabolic adverse effects, anticholinergic activity, and activity on serum prolactin. The agent is less sedating then other antipsychotic medicines. Aripiprazole has benefits in patients who do not require sedation and who may be at risk of weight gain and metabolic syndrome. Due its partial agonist properties, aripiprazole when combined with other antipsychotics, can reduce dopamine binding and cause breakthrough psychosis.

- **Ziprasidone:** has low sedation but there have been reports of Parkinson-like adverse effects. It has lower antipsychotic potency so has been used in patients with more mild schizophrenic illness. Ziprasidone has little effect on weight gain so is useful in patients at risk of metabolic syndrome.
References

1. Medsafe Data Sheets
2. Psychotropic Drug Directory 2010 S Bazire