**Second Generation antipsychotics**

Antipsychotics are mostly used to treat the symptoms of psychosis in mental health disorders such as schizophrenia and bipolar disorder. In lower doses they may be used for sedation, sleep and easing anxiety. Some newer antipsychotics also have antidepressant effects. Excessive levels of a chemical called dopamine in certain areas of the brain is largely responsible for the symptoms of psychosis in conditions like schizophrenia and bipolar disorder. Antipsychotics mainly block the brain’s dopamine receptors thus reducing dopamine which leads to an antipsychotic effect. Second Generation Antipsychotics are the second most common class of drugs prescribed for mental health problems after antidepressants. For the purpose of this article I will refer to Second Generation Antipsychotics as SGAs for short.

**Difference between SGAs and FGAs**

The main difference between older First Generation Antipsychotics (FGAs) and newer Second Generation Antipsychotics (SGAs) relates to the ability of the medication to block the effects of dopamine on the brain. The older FGAs cause more dopamine blockage, hence more side effects. First generation antipsychotics (FGAs) available in Ireland include Chlorpromazine (Clonactil®, Largactil®), Haloperidol (Serenace®), Trifluperazine (Stelazine®), Zuclopenthixol (Clopixol®) and flupentixol (Depixol® Injection, Fluanxol® tablets). FGAs were first developed in the 1950s while most SGAs came on the market in the 1990s. They are all prescription only medicines and are usually initially prescribed by experts in mental health such as clinical psychologists. I have more information on First generation antipsychotics (FGAs) in the pharmacy or at www.whelehans.ie.

The newer atypical antipsychotics (SGAs) still block dopamine, but much less so than the older FGAs. SGAs also tend to have an effect on different chemical messengers in the brain compared to FGAs including serotonin. Because SGAs have less effect on dopamine receptors, they are less likely to cause extrapyramidal symptoms (EPS) such as muscle tremors and muscle stiffness and rigidity. There is also less chance of movement disorders including akathisia (a kind of EPS characterized by a sense of restlessness, inability to sit still, nervousness, muscle discomfort and agitation), dystonia (another kind of EPS which include sudden spasm of muscles usually affecting the tongue, jaw and neck) and tardive dyskinesia (an involuntary movement disorder which includes involuntary and continual movements of the mouth, tongue and jaw). Second generation anti-psychotics (SGAs) available in Ireland include risperidone, quetiapine and olanzapine.

**Side-effects of SGAs**

The most common side effects of SGAs include sleepiness and slowness, weight gain, interference with your sex life, increased chance of developing diabetes.In high doses, some have the same parkinsonian side-effects as the older medications. Long-term use can produce movements of the face (tardive dyskinesia) and, rarely, of the arms or legs.

Compared to the older drugs they seem less likely to cause parkinsonian side-effects (see above), less likely to produce tardive dyskinesia, more likely to produce weight gain, more likely to produce diabetes andmore likely to give you sexual problems.

One of the main issues with SGAs compared with FGAs is the risk of weight gain. This weight gain increases the risk of developing diabetes and heart problems (including raised cholesterol)in the longer term thus blood sugars and cholesterol levels should be monitored regularly. Weight gain appears to be a particular problem with clozapine and olanzapine. For example, trials show that olanzapine can cause weight gain of 5.4kg within 5 weeks of treatment and weight gain of 20kg or more after longer term treatment. Ziprasidone (Geodon®) and amisulpride (Solian®) tend to cause less weight gain than other SGAs.SGAs can sometimes cause the tendency to cause obsessive compulsive symptoms.

**Are SGAs really advantageous over FGAs?**

Oral SGAs account for approximately 73% of antipsychotic medication prescribed. Advantages claimed for these newer SGAs when they came out initially in the 1990s included better efficacy for negative as well as positive symptoms (FGAs are less effective for negative symptoms), mood, reduced neurological side effects and cognitive enhancement. Positive symptoms of mental health problems such as schizophrenia include hallucinations, irrational thoughts and hostility. However, experience and studies have since indicated that the perceived advantages of SGAs over FGAs are not as strong as initially perceived in the early 1990s when SGAs first came out. Drug trials of second generation antipsychotics initially conducted by manufacturers of SGAs have been heavily criticized for being short-term and using participants not representative of patients encountered in actual practice. However, SGAs appear to be more effective than older FGA for negative symptoms of schizophrenia (eg) Emotional and social withdrawal, flat affect, lack of spontaneity, inability to feel pleasure, attention impairment, poor self-care, poor motivation, lack of interest and other restrictions in thought, speech, and behaviour. Two influential clinical trials, CATIE and CUtLASS, indicated that the benefits of SGAs over FGAs (if any) were not as significant as first thought.

**Clozapine**

Clozapine seems to be the only antipsychotic medication which works better than any of the others. It also seems to reduce suicidal feelings in people with schizophrenia. It has many of the same side-effects as other newer antipsychotics, but can also appears to have more of a tendency to cause the patient to produce more saliva. It is different in that it seems to have very little, if any, effect on the dopamine systems which control movement, and so causes hardly any of the stiffness, shakiness or slowness experienced with other antipsychotics. Although it does tend to cause drowsiness, some people are prepared to put up with this because it makes them feel less sluggish than on the older antipsychotics. It also does not seem to produce the longer-term problem of tardive dyskinesia.

**Side-effects of Clozapine**

The main drawback of clozapine is that it can affect bone marrow, leading to a shortage of white cells. This can make a patient vulnerable to infection. If this happens, the medication is stopped at once so that the bone marrow can recover. Initially when taking Clozapine, weekly blood tests are required for the first 6 months and 2 weekly blood tests after that. It can also cause weight gain, over-production of saliva and make epileptic fits more likely. These problems mean that Clozapine is reserved for patients with schizophrenia who have not responded well to the use of two or more antipsychotics (one of which should be an SGA) each for at least 6–8 weeks.It is a difficult drug to monitor and can be difficult to take, but some people find that it gives them a much better quality of life.

**Long Acting Injections**

There are five FGA depot injections and two SGAs (risperidone (Risperdal Consta®) and paliperidone (Xeplion®)) available in Ireland as a long-acting injection.

**Second-generation long-acting antipsychotic injections**

**Risperidone injection**

Risperidone was the first second generationLAI to be licensed in the UK and Ireland. Therisperidone LAI antipsychotic works in a different way to the first-generation depot injections. The drug will not reach a therapeutic level for a few weeks after injection; therefore it is essential that the patient receive alternative antipsychotic medication during the initial period of treatment following the first injection.

**Paliperidone injection**

Xeplion® injections contain the active ingredient paliperidone. Paliperidone blocks serotonin 5-HT2 and dopamine D2 receptors.Dopamine and serotonin are neurotransmitters known to be involved in regulating mood and behaviour, amongst other things. People with schizophrenia may experience 'positive symptoms' (such as hallucinations, disturbances of thought, hostility) and/or 'negative symptoms' (such as lack of emotion and social withdrawal). Paliperidone is effective in relieving both positive and negative symptoms of schizophrenia, whereas older antipsychotics are usually less effective against the negative symptoms. Paliperidone also relieves 'affective symptoms' that are associated with schizophrenia, such as depression, guilt feelings or anxiety. Xeplion® injection is administered into the muscle of the upper arm or buttock, where it forms a reservoir of medicine that is slowly released into the bloodstream. The injection is given once every four weeks.

**Patient suitability:**

Paliperidone LAI has not been shown to be any more efficacious than risperidone long acting injection but does have some practical advantages including the fact it does not have to be stored in the fridge, it only has to be administered once monthly and comes as a pre-filled syringe meaning administration is easier and quicker. There are no data on efficacy in prevention of relapse relative to other long acting injections.

**Role of SGAs in depression**

Major depressive disorder (MDD) is a common condition with 15% to 18% of the population suffering from major depression at some stage in their life. Some antipsychotics have been reported to give relief in major depression, when added to an antidepressant. Generally, treatment with second-generation antipsychotic drugs are less well tolerated by the patient, mainly due to sedation, weight gain or laboratory values such as prolactin increase. Second-generation antipsychotics for major depressive disorder should only be considered as last line if conventional anti-depressants fail to control symptoms.

**Use of SGAs for anxiety disorders**

Anxiety disorders are common and disabling conditions with 17% of the general population suffering from anxiety at some stage of their lives. Due to high rates of treatment resistance, there is interest in new pharmacological treatment options such as second-generation antipsychotics. Sedative-hypnotics (eg. Diazepam) are commonly prescribed for anxiety disorders but are frequently reserved for short durations and targeted symptoms (e.g., insomnia) because of the potential for abuse, dependency, withdrawal reactions, and cognitive impairment. The role for antipsychotic drugs in the treatment of anxiety disorders, however, is less clear because of the relative lack of well-designed trials to assess their safety, efficacy, and effectiveness.

According to a 2011 editorial in the American Journal of Psychiatry, there is a lack of evidence in the scientific literature for the use of antipsychotics as a first-line treatment for anxiety disorders, but there is support for their role as an add on treatment of resistant obsessive-compulsive disorder and posttraumatic stress disorders. The largest increase in antipsychotic treatment reported in the study was for panic disorder, which is another anxiety disorder that is associated with inadequate efficacy for many patients treated with first-line therapies such as anti-depressants.

**Role of SGAs for Bipolar disorder**

**Management of the manic phase of Bipolar disorder**

Only lithium, olanzapine, quetiapine, risperidone and valproate are licensed for the treatment of acute mania in the Ireland. Mania is the “high” phase that people suffering from bipolar disorder can experience; it is usually followed by period of deep depression. If a patient is taking an antidepressant at the onset of an acute manic (high) episode, the antidepressant should be stopped as the antidepressant can make the manic phase worse. This may be done abruptly or gradually, depending on the patient’s current clinical need and previous experience of discontinuation/withdrawal symptoms.

**Drug treatment for acute mania for people not taking anti-manic medication**

If a patient develops acute mania when not taking anti-manic medication, treatment options include starting an antipsychotic (olanzapine, quetiapine, and risperidone), valproate or lithium. When making the choice, prescribers should consider prescribing an antipsychotic if there are severe manic symptoms or marked behavioural disturbance as part of the syndrome of mania. Valproate or lithium can be prescribed if symptoms have responded to these drugs before. Valproate should be avoided in women of child-bearing potential. Lithium should only be used if symptoms are not severe because it has a slower onset of action than antipsychotics and valproate. Initially, if the person is severely agitated, the short-term use of a benzodiazepine, such as lorazepam (Ativan®) should be considered in addition to the anti-manic agent.

If treating acute mania with antipsychotics (olanzapine, quetiapine or risperidone), the following should be taken into account: \*Individual risk factors for side effects (such as the risk of diabetes). \*Start at the lowest possible dose and increase slowly according to response. \*If an antipsychotic proves ineffective, adding valproate or lithium should be considered. \*Older people are at greater risk of sudden onset of depressive symptoms after recovery from a manic episode. \*Carbamazepine should not be routinely used for treating acute mania. It should only be used if the person cannot tolerate lithium.

**Drug treatment of acute mania for people already taking anti-manic medication**

*If currently taking anti-psychotic***:** If a patient already taking an antipsychotic experiences a manic episode, the dose should be checked and increased if necessary. If there are no signs of improvement, the addition of lithium or valproate should be considered.

*If currently taking lithium:* If a patient already taking lithium experiences a manic episode, plasma lithium levels should be checked. If levels are suboptimal (that is, below 0.8 mmol per litre), the dose should normally be increased to a maximum blood level of 1.0 mmol per litre. If the response is not adequate, adding an antipsychotic to lithium should be considered.

*If currently taking valproate:* If a patient already taking valproate experiences a manic episode, the dose should be increased until the symptoms start to improve or side effects limit further dose increase. If there are no signs of improvement, the addition of olanzapine, quetiapine, or risperidone should be considered.

*If currently taking carbamazepine:*

For patients who present with mania when already taking carbamazepine, the dose should not routinely be increased. Adding an antipsychotic should be considered, depending on the severity of mania and the current dose of carbamazepine. Interactions with other drugs are common with carbamazepine so must be considered.

**Treatment of depressive symptoms in bipolar disorder**

Managing acute depressive symptoms in bipolar disorder has some similarities to managing depression in people who are not bi-polar (uni-polar depression). However, in bipolar disorder, antidepressants carry the risk of bringing on manic states. There is only a limited role for long term treatment with antidepressants in bipolar depression; preventative medication has a greater role.

**Patients not taking anti-manic medication**

A patient who is prescribed antidepressant medication should also be prescribed an anti-manic drug. Antidepressant treatment should begin at a low dose and be increased gradually if necessary.

**Patients taking anti-manic medication**

If a person has an acute depressive episode when taking anti-manic medication, prescribers should first check they are taking the anti-manic agent at the appropriate dose and adjust the dose if necessary. For patients with moderate or severe depression, prescribers should normally consider prescribing an SSRI antidepressant (eg. fluoxetine, citalopram, escitalopram, but not paroxetine in pregnant women). Quetiapine should be added if the patient is already taking anti-manic medication that is not an antipsychotic. (eg) lithium, valproate.

**Options if depression does not respond to antidepressant**

When depressive symptoms do not fully respond to an antidepressant, the person should be reassessed for evidence of substance misuse, physical health problems, other psychological disorders such as anxiety or severe obsessional symptoms, and whether the person is taking their medication properly. Prescribers should then consider: \*increasing the dose of the antidepressant \*switching to an alternative antidepressant (eg) mirtazapine (Zispin®, Mirap®) or venlafaxine (Efexor XL®, Vensir XL®) \*adding quetiapine or olanzapine if the patient is not already taking one of these, or adding lithium if the patient is not already taking it. If depressive symptoms have failed to respond to at least three courses of treatment for depression of adequate dose and duration, the person should be referred to a specialist in bipolar disorder.

**Use of anti-psychotics for agitated behaviour in the elderly**

In 2004 the Committee on Safety of Medicines in the UK first reported a clear increase in the risk of stroke with the use of risperidone and olanzapine in elderly people with dementia. In 2005 a Europe-wide review concluded that the risk could not be excluded for other SGAs or FGAs. An extended follow up trial called the dementia antipsychotic withdrawal trial (DART-AD) found that patients with Alzheimer’s dementia who continued to use antipsychotics were more likely to die than those not taking an antipsychotic drug. The difference were quite startling, at 24 months, survival was only 46% for those prescribed antipsychotics compared to a survival rate of 71% for those who were not. At 36 months’ survival rate was only 30% for those prescribed anti-psychotics as opposed to a 59%.survival rate for those who were not. Warnings from the European Medicines Agency and the Medicines and Healthcare products Regulatory Authority reiterate the increased risk of stroke and a small increased risk of death when any antipsychotics are used in elderly people with dementia. The NICE (main UK health advisory body) guidance on dementia advise that antipsychotics are only to be used in exceptional circumstances in such patients.

**Disclaimer: Please ensure you consult with your healthcare professional before making any changes recommended**

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