Journal of Pharmacy and Alternative Medicine
ISSN 2222-5668 (Paper) ISSN 2222-4807 (Online)
Vol. 2, No. 4, 2013

Review Article

Antipsychotic drugs: A review with a focus on QT prolongation

Peter T. Zolas[1] and Alam Sher[2-6]*

[1]Peter T. Zolas, PGY 1 Pharmacy Resident, Pharmacy Service, VA Maine Health Care System, Augusta, Maine, USA

[2]Mental Health Clinical Pharmacist, VA Maine Healthcare System, Augusta, Maine, USA

[3]Clinical Associate Professor of Family Medicine (Psychiatry), College of Osteopathic Medicine of the UNE, Maine, USA

[4]Adjunct Associate Professor of Pharmacy Practice, Massachusetts College of Pharmacy and allied Sciences, Boston, USA

[5]HEC Visiting Scholar, College of Pharmacy of the Islamia University, Bahawalpur, Pakistan

[6]Co-founder and V. President of the Nasreen and Alam Sher Foundation, Chelsea, Maine

*E-mail of the corresponding author: Alam.Sher2@va.gov

Accepted Date: 15 November 2013

Abstract

Antipsychotic medications are effective in the treatment of acute psychosis, irrespective of cause, chronic psychotic disorders, and other psychiatric and non-psychiatric conditions. They are categorized into first-generation antipsychotics (FGAs), also known as “typical” antipsychotics, and second-generation antipsychotics (SGAs), or otherwise known as “atypical” antipsychotics. This review article summarizes both typical and atypical antipsychotics, as well as, examines the mechanism and propensity of these agents to prolong the QTc interval.

Keywords: Chlorpromazine, Clozapine, Antipsychotic History, Typical and Atypical Antipsychotics, Psychopharmacotherapy, Psychiatry, QTc, Schizophrenia

1. Background: History of antipsychotic drug development (Shen, 1999)

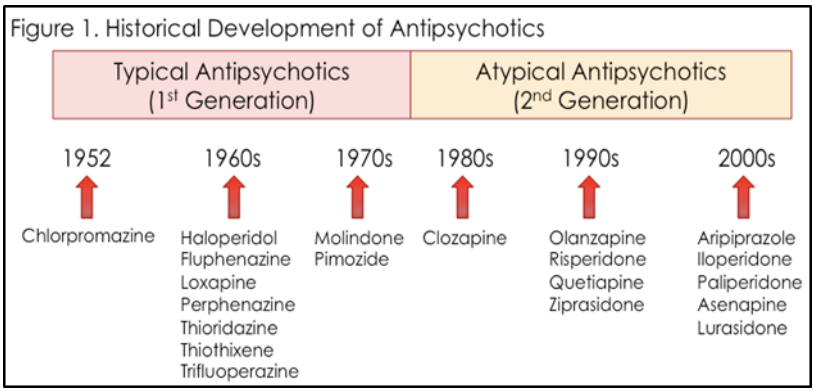
The history of antipsychotics in treating psychotic disorders is based on chance findings after chlorpromazine was administered to patients for its potential anesthetic effects during surgeries in 1951 (Laborit et al., 1952). Shortly thereafter, researchers discovered their antipsychotic activity following their use in psychiatric patients (Ban, 2007), and soon several first generation or typical antipsychotics were introduced to the world market (Ban et al., 1998). It was not until late the 1980s, that we were introduced to "atypical" antipsychotic drugs, with the approval of clozapine. Clozapine was found to be more effective in treating schizophrenia than FGAs, and carried significantly less risk of developing extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) (Kane et al., 1988). However, other side effects, specifically agranulocytosis, a serious, life-threatening condition, limited its use (Jose et al., 1993; Alvir et al., 1993). Therefore, development continued in order to discover safer atypical antipsychotics, and they have now replaced FGAs as standard of care for schizophrenia.

2. Introduction and Indications

Schizophrenia is a psychiatric disorder involving chronic or recurrent psychosis that typically impairs social and occupational functioning. Schizophrenia is believed to occur due to excess dopamine in the mesolimbic pathway. Excess dopamine causes a deficit in sensory gating, and often patients become hyper vigilant and respond to extraneous stimuli that others typically ignore. Positive symptoms associated with schizophrenia include hallucinations or delusions, disorganized speech, negative symptoms such as a flat affect or poverty of speech, and impairments in cognition including attention, memory and executive functions. Schizophrenia is diagnosed based on the presence of such symptoms, along with the presence of social or

occupational dysfunction for at least six months, in the absence of another diagnosis that would better account for the patient's symptoms. Differential diagnoses include, but are not limited to, medications, such as corticosteroids, anticholinergics, and dopamine agonists, infection, tumor, endocrine disorder (elevated thyroid function), temporal lobe epilepsy, and illicit drug use, such as cocaine, alcohol, amphetamines, and/or hallucinogens. During adolescence, one may experience prodrome symptoms, such as having difficulty relating to others or being socially awkward. The onset of schizophrenia typically occurs in the third or fourth decades of life, with earlier onset in males versus females. It is a chronic disease, with episodes of remission and relapse, with residual symptoms in between relapses.

Figure 1. Historical Development of Antipsychotics



Schizophrenia is categorized into five subtypes, catatonic, disorganized, paranoid, undifferentiated, and residual. Catatonic schizophrenia includes episodes of behavior at extreme opposite ends of the behavioral spectrum. For instance, one may be in coma-like daze, unable to speak, move or respond; they are resistant to movement and are in a 'catatonic stupor'. On the other end of the spectrum, they may talk and behave in a bizarre, hyperactive way. Catatonic episodes may last for a month or longer without treatment, but this type of schizophrenia is rare now that we are able to utilize antipsychotics. Disorganized schizophrenia is considered a more severe type of schizophrenia, in which ones' thoughts, speech and behavior are inappropriate and don't make sense. These patients may have difficulty performing routine daily activities, such as bathing themselves, and cooking a meal. Paranoid schizophrenia is the most common type of schizophrenia, characterized by relatively stable, often paranoid, delusions, usually accompanied by hallucinations, particularly of the auditory variety, and perceptual disturbances. Patients with paranoid schizophrenia may be more capable in performing functions of daily living than other forms of schizophrenia. However, this form of schizophrenia can lead to many complications, including suicidal behavior. Residual schizophrenia is characterized by a past history of at least one episode of schizophrenia, but the person currently has no "positive" symptoms (e.g. delusions, hallucinations, disorganized speech, or behavior). Undifferentiated schizophrenia is characterized by some symptoms seen in all of the above types, but not enough of any one of them to define it as another particular type of schizophrenia (DSM-IV-TR). The cardinal goals of treatment with antipsychotic medications are to reduce the frequency and severity of psychotic exacerbations, ameliorate symptoms, and improve functional capacity and quality of life.

Schizophrenia is categorized into five subtypes, catatonic, disorganized, paranoid, undifferentiated, and residual. Catatonic schizophrenia includes episodes of behavior at extreme opposite ends of the behavioral spectrum. For instance, one may be in coma-like daze, unable to speak, move or respond; they are resistant to movement and are in a 'catatonic stupor'. On the other end of the spectrum, they may talk and behave in a bizarre, hyperactive way. Catatonic episodes may last for a month or longer without treatment, but this type of schizophrenia is rare now that we are able to utilize antipsychotics. Disorganized schizophrenia is considered a more severe type of schizophrenia, in which ones' thoughts, speech and behavior are inappropriate and don't make sense. These patients may have difficulty performing routine daily activities, such as bathing themselves, and cooking a meal. Paranoid schizophrenia is the most common type of schizophrenia, characterized by relatively stable, often paranoid, delusions, usually accompanied by hallucinations, particularly of the auditory variety, and perceptual disturbances. Patients with paranoid

schizophrenia may be more capable in performing functions of daily living than other forms of schizophrenia. However, this form of schizophrenia can lead to many complications, including suicidal behavior. Residual schizophrenia is characterized by a past history of at least one episode of schizophrenia, but the person currently has no "positive" symptoms (e.g. delusions, hallucinations, disorganized speech, or behavior). Undifferentiated schizophrenia is characterized by some symptoms seen in all of the above types, but not enough of any one of them to define it as another particular type of schizophrenia (DSM-IV-TR).

The cardinal goals of treatment with antipsychotic medications are to reduce the frequency and severity of psychotic exacerbations, ameliorate symptoms, and improve functional capacity and quality of life

Table 1. Schizophrenia Subtype

Type	Description
Catatonic	• Episodes of behavior at extreme opposite ends of the behavioral spectrum • Rare now that can treat schizophrenia
Disorganized	• Thoughts, speech and behavior that are inappropriate and don't make sense
Paranoid	• Most common form • Delusions or hallucinations (typically auditory) • Least functional impairments with the best prognosis. However, has the highest suicide
Residual	• History of at least one episode of schizophrenia, but no current positive symptoms
Undifferentiated	• No defined symptoms to place in one particular subtype listed above

3. First-generation antipsychotics (FGAs)

First-generation antipsychotics (FGAs), also known as neuroleptics, major tranquilizers, or “typical” antipsychotics, are effective in treating positive symptoms but are ineffective in treating negative or cognitive symptoms associated with schizophrenia. FGAs work by antagonizing dopamine at D2 receptors throughout the brain, and binding is highly correlated with clinical potency (Seeman, 2002) and side effects such as movement disorders and elevated prolactin levels. Besides their activity at D2 receptors, each FGA has a distinct effect on alpha adrenergic (α) and muscarinic acetylcholine receptors (mAChRs or metabotropic), leading to additional side effects associated with these agents. FGAs are lipophilic, highly protein and tissue-bound compounds with large volumes of distribution and fairly long half-lives. They undergo extensive metabolism via cytochrome P450 (CYP) enzymes, and several agents have active metabolites. Therefore, drug-drug interactions can occur with the co-administration with potent cytochrome P450 (CYP) inhibitors or inducers. Most FGAs are available in oral formulations. However, several are also available as injectable, intramuscular (IM) formulations, which are useful in the treatment of psychotic agitation. In addition, long-acting decanoate formulations of haloperidol and fluphenazine can be administered via intramuscular injection one to two times per month for those patients who are

non-adherent with daily oral dosing. First generation antipsychotics have traditionally been classified by their chemical structure (eg, phenothiazines, butyrophenones, thioxanthenes).

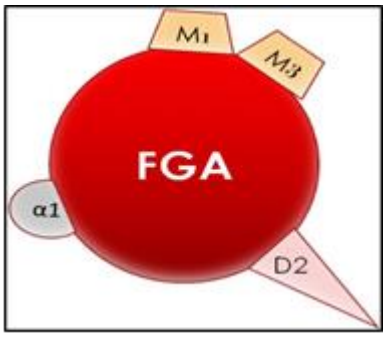


Figure 2: FGA receptor binding

However, differences between chemical classes do not translate into differences in drug efficacy, side effects, or types of patients that respond. For the majority, FGAs have comparable efficacy in the treatment of psychosis. What they differ in is their side effect profile, which is captured in the classification of these agents as either high- or low-potency. High potency antipsychotics tend to be less histaminergic, alpha adrenergic and anticholinergic. Meaning they are less sedating (histaminergic), they do not cause as much blurred vision, urinary retention, dry mouth, or constipation (anticholinergic), or orthostatic hypotension (alpha adrenergic) when compared to low potency FGAs. High potency FGAs also carry a low to moderate risk of weight gain, but a higher risk of developing EPS and neuroleptic malignant syndrome (NMS).

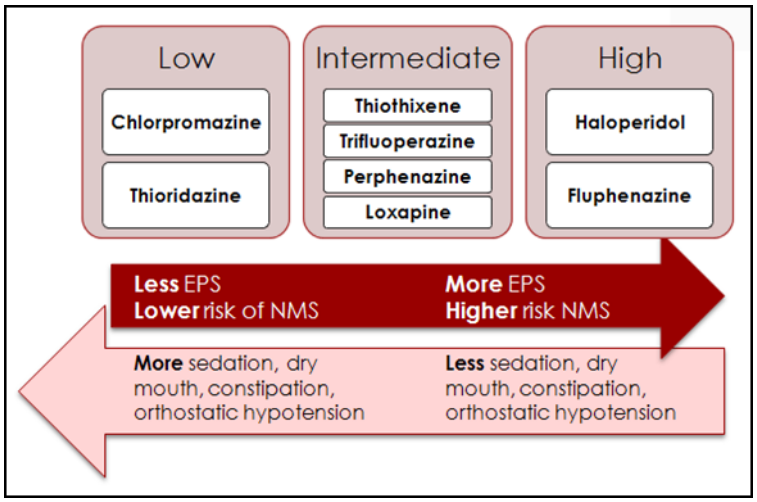


Figure 3: FGA classification by potency

3.1 High potency FGAs

Haloperidol (Haldol®) is the most extensively studied and remains the most widely used FGA. It is available as an oral tablet, solution or short-acting injectable formulation for IM and intravenous (IV) use. It is also available as a long acting decanoate depot injection given intramuscularly at a dose of 25 to 100 mg every 4 weeks. Although, haloperidol is absorbed orally, its bioavailability is reduced (60%) because of extensive first-pass hepatic metabolism. It is cleared by cytochrome P450 isoenzymes CYP3A4 and CYP2D6, and glucuronidation, with a half-life of about 20 hours (oral formulation) (Kudo and Ishizaki, 2002). It can interact with potent inhibitors or inducers of these cytochrome P450 isoenzymes, with notable elevated levels when administered with fluoxetine, paroxetine, and bupropion, and decreased levels with

carbamazepine. Many times, the interactions can be managed with dose adjustments. Drug interactions with medications that can also prolong the QTc interval should be taken into consideration. Given its classification as a high potency FGA, haloperidol carries an increased risk of developing EPS. As a way to prevent the development of EPS, the dose of oral haloperidol has decreased over the years, and is currently being used at doses of 10 to 20 mg/day. Doses of IM injection, for the treatment of agitation associated with psychosis, typically ranges from 2 to 10 mg, given as often as every 30 minutes with effects peaking at 20 minutes after administration.

Fluphenazine (Prolixin®) is a phenothiazine piperazine that is clinically comparable to haloperidol in most regards, with similar efficacy, potency, routes of administration, dosing, and side effects. It is available as oral tablets, solution or IM injection and the typical dose range is 2 to 20 mg/day. Like haloperidol, it also comes in a long-acting decanoate injection (IM) given at a dose of 6.25 to 50mg every 2 weeks. Of all depot injections though, fluphenazine is most likely to "dump", or release the drug into the body all at once. The half-life of oral fluphenazine has been reported to be as high as 33 hours (Midha et al., 1983), and the half-life of fluphenazine decanoate is around 14 days. Fluphenazine is metabolized primarily in the liver via cytochrome P450 isoenzyme CYP2D6.

3.2 Intermediate potency FGAs

Intermediate potency FGAs tend to have a more moderate side effect profile when compared to high potency FGAs. Thiothixene (Navane®), a thioxanthene compound, is only available as an oral capsule, dosed 4 to 40 mg administered at least twice daily. Efficacy, dosing, and side effects are indistinguishable from haloperidol. Trifluoperazine (Stelazine®) is a phenothiazine piperazine, available as an oral tablet, dosed 4 to 40 mg administered twice daily. It may also be used for non-psychotic anxiety, at lower doses, such as 1-2 mg twice daily. Perphenazine (Trilafon®), a piperazinyl phenothiazine, is available as an oral tablet dosed 10 to 64 mg administered twice daily. It is also available as combination tablet with amitriptyline, approved for use in depression, anxiety, and agitation. Perphenazine is metabolized via multiple metabolic pathways, thus leading to potentially fewer drug-drug interactions. Another clinical advantage, perphenazine has a lower rate of EPS compared to haloperidol, and a comparable rate to risperidone, a second generation antipsychotic (Coley et al., 1999). Loxapine (Loxitane®), a dibenzoxazepine, is available as an oral capsule dosed 10 to 80 mg daily, divided into at least two daily doses. The efficacy and side effect profile of loxapine is similar to haloperidol with one exception, in that it may cause less weight gain.

3.3 Low potency FGAs

Chlorpromazine (Thorazine®), a phenothiazine, was the first antipsychotic on the market in the 1950s. Newer antipsychotics have since replaced chlorpromazine due to its side effect profile, and newer antiemetics that have better efficacy and fewer side effects have superseded chlorpromazine's use in this area as well. Chlorpromazine is available as an oral tablet and solution and an IM injection, dosed 100 to 800 mg/day. Single injectable doses for acute agitation are usually 50 to 200 mg. Thioridazine (Mellaril®), a piperidine phenothiazine, is available as an oral tablet dosed 100 to 800 mg/day. A unique adverse effect associated with thioridazine is retinitis pigmentosa when used at high doses. Also, thioridazine is associated with a higher risk of QT prolongation and lethal torsade de pointes (TdP) when compared to other antipsychotics. As a result, it has been discontinued in some countries, and is reserved only after failed trials of other antipsychotics, in the U.S.

4. Second-generation antipsychotics (SGAs)

Second-generation antipsychotics (SGAs), also known as "atypical" antipsychotics, are similar to FGAs in that they also work by blocking D2 receptors. However, SGAs differ from FGAs in that serotonin 5HT2 receptor binding can exceed their affinity for dopamine D2 receptors. Furthermore, aripiprazole is unique, in that it also acts as a partial D2 agonist. The differences in affinity for other neurotransmitter receptors help explain some of the differences in SGAs' side effect profile and the mood and cognitive benefits one may get with their use. However, one author believes that SGAs' low-affinity and fast dissociation from the dopamine D2 receptor, along with the administration in doses that provide adequate levels of dopamine D2 receptor blockade lead to their "atypicality", rather than their actions on neurotransmitter receptors besides

D2 (Kapur and Remington, 2001). In general, SGAs have minimal effect on serum prolactin and carry a lower risk of EPS and tardive dyskinesia compared to FGAs. However, SGAs may cause higher rates of weight gain and metabolic side effects, varying in their degree depending on the agent. Although, SGAs have replaced FGAs as the standard of care, the question of whether they are more effective than FGAs remains uncertain. In large-scale studies, such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Lieberman et al., 2005) and the European First Episode Schizophrenia Trial (Kahn et al., 2008), they found that SGAs may be no more effective than FGAs. In any case, it is known that SGAs are associated with a better safety profile, possibly leading to better adherence to treatment, and is an option for those patients who are labeled as treatment-refractory to FGAs. As far as comparing efficacy between SGAs, all have similar efficacy, with the exception of clozapine, which has an advantage in treating refractory schizophrenia.

Table 2: SGA side effect profiles

	Weight gain/ diabetes mellitus	Hyper-cholesterolemia	EPS/TD	Prolactin elevation	Sedation	Anti-cholinergic side effects	Orthostatic hypotension
Aripiprazole	–	–	+	–	+	–	–
Asenapine	+	–	+	++	++	–	+
Clozapine	+++	+++	–	–	+++	+++	+++
Iloperidone	++	++	+	–	+	+	+++
Lurasidone	–	–	+	+	++	–	+
Olanzapine	+++	+++	+[b]	+[c]	++	++	+
Paliperidone	++	+	++	+++	+	–	++
Quetiapine	++	+++	–	–	++	+	++
Risperidone	++	+	++[a]	+++[c]	+	–	++
Ziprasidone	–	–	+	+	+	–	+

a: very low at dosages < 8 mg/day b: with dosages < 20 mg/day c: dose related

All SGAs are available as oral tablets or capsules, and like FGAs, many are available as injectable, IM formulations, useful in the treatment of psychotic agitation. In addition, long-acting decanoate formulations of risperidone, paliperidone, aripiprazole, and olanzapine are available.

Table 3: SGA dosing and formulations

Drug	Typical Dose	Formulations	Acute Agitation	Depot Injection
Risperidone (Risperdal ®)	0.25-6 mg once daily	T, RDT, SOL, IM	×	×
Paliperidone (Invega®)	6-12 mg once daily	T (ER)		×
Quetiapine (Seroquel®)	300-800 mg divided BID or once daily	T (IR & ER)		
Olanzapine (Zyprexa®)	2.5-20 mg once daily	T, RDT, IM	×	×
Ziprasidone (Geodon®)	120-200 mg, divided BID; w/ food	C, IM	×	
Aripiprazole (Abilify®)	5-20 mg once daily	T, RDT, SOL, IM	×	×
Clozapine (Clozaril®)	400-600 mg daily	T, RDT		
Iloperidone (Fanapt®)	6-12 mg divided BID	T		
Asenapine (Saphris®)	5 mg BID	T (SL)	×	

T – tablet; RTD – rapid disintegrated tablet; C – capsule; SOL – oral solution; IM – intramuscular injection; IR – immediate release; ER – extended release; SL - sublingual

5. QT Prolongation

The QT interval is the length of time from the start of the Q wave to the end of the T wave, and represents the time it takes for ventricular depolarization and repolarization. It is inversely proportional to heart rate, meaning the interval is shortened at faster heart rates and lengthened at slower heart rates. Because of this, the interval duration is usually corrected for heart rate and referred to as the QTc interval. Normal QTc values are not universally established due to multiple variables that affect its measurement such as gender, time of day, diet, heart rate, and lead selection when measuring. However, an interval below 440ms is generally considered to be normal. It is when the interval lengthens, that the risk of torsade de pointes (TdP), a polymorphic ventricular tachycardia, increases. Generally, the normal upper limit for QTc is considered to be 450ms for men and 460ms for women, and a QTc interval of > 500 ms is considered to be a substantial risk factor for TdP (Moss and Robinson, 1992). Also, clinicians should be concerned with a greater than 25% increase in the QTc interval from baseline.

Schizophrenia and other psychiatric disorders are associated with an increased risk of cardiovascular disease and higher baseline QTc intervals relative to the general population. In addition, there are well-established concerns over QTc prolongation and the development of life-threatening arrhythmias, with the use of antipsychotic drugs. It is important for clinicians to recognize the risks associated with QTc prolongation in order to prevent arrhythmias, especially those caused by drugs including certain antibiotics, antiarrhythmics, selective serotonin receptor inhibitors (SSRI), and other medications such as methadone. Other risk factors for QTc prolongation include but are not limited to age above 65 years old, female gender, congenital long QT syndrome (LQTS), personal or family history of LQTS, cardiovascular disease, and electrolyte disturbances (i.e. hypokalemia, hypomagnesemia, hypocalcaemia).

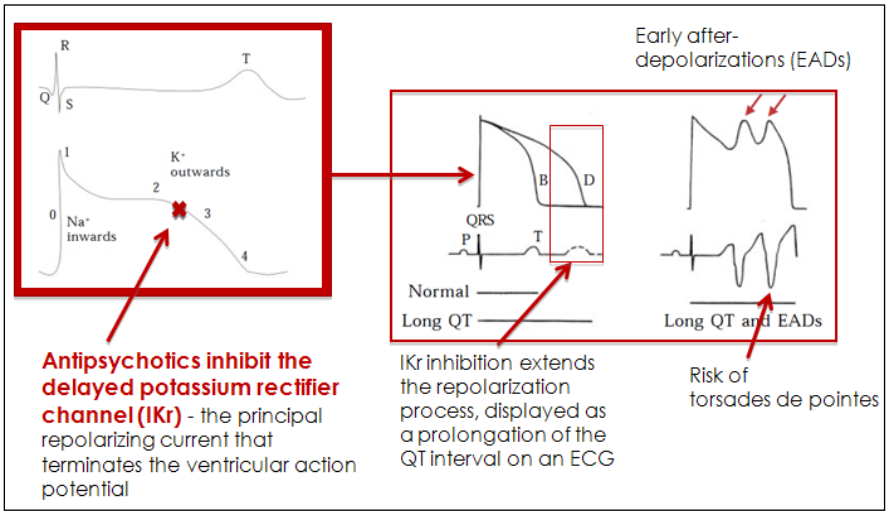


Figure 4: QTc prolongation MOA

The QT prolonging tendency of antipsychotics is based on the capacity to inhibit the cardiac delayed potassium rectifier channel (IKr) (Sanguinetti et al., 1995; Yang and Roden, 1996). The inhibition of IKr extends the repolarization process of the ventricles of the heart, displayed as a prolongation of the QT interval on an electrocardiogram (ECG). This blockade may cause enough prolongation to generate extra potentials that may lead to premature ventricular beats capable of triggering TdP and sudden cardiac death (SCD).

Crumb and colleagues studied the effects of haloperidol, olanzapine, risperidone, thioridazine, and ziprasidone on several ionic currents that contribute to changes in the action potential in cardiac tissue. They found that the blockade of the hERG, a K+ channel gene, ion channel is the likely mechanism for the prolongation of the QT interval. In addition they found relatively modest increases in QTc prolongation during treatment with olanzapine, risperidone, and haloperidol (1.7, 3.6, and 7.1 msec, respectively), and

more pronounced increases for ziprasidone and thioridazine (15.9 and 30.1 msec, respectively) (Crumb W, et al. 2006).

As a class, typical antipyschotics seem to prolong the QTc interval more so than atypical antipsychotics, and in general, low potency typical antipsychotics are thought to carry a greater risk than high-potency agents. This risk is thought to be dose related. The best available data comes from a randomized, prospective study, that Pfizer did at the FDA's request, comparing the effects of six antipsychotics on the QTc interval at and around the time of estimated peak plasma/serum concentrations in medically healthy individuals with psychotic disorders (Harrigan EP, et al 2004). Thioridazine (at a moderate dose of 300 mg/day) showed the greatest prolongation of the QTc compared with ziprasidone (160 mg/d), risperidone (up to 16 mg/d), olanzapine (20 mg/d), quetiapine (750 mg/d), or haloperidol (15 mg/d). In addition, this study found that inhibition of the major CYP450 pathways for each antipsychotic studied did not result in large increases in drug levels (except for quetiapine) or augmentation of QTc prolongation. The authors suggested the reason being that alternative metabolic pathways might share responsibility for drug clearance for these agents.

Table 4: Effects of antipsychotics on the QTc interval

Drug	Baseline (mean)	Change At Steady State (msec)	
		mean	95% CI
1st Generation Antipsychotics			
Thioridazine	395.9	35.6	30.5 to 40.7
Haloperidol	394.7	4.7	-2.0 to 11.3
2nd Generation Antipsychotics			
Ziprasidone	402.1	20.3	14.2 to 26.4
Risperidone	396.3	11.6	7.4 to 15.8
Olanzapine	397.9	6.8	0.8 to 12.7
Quetiapine	398.0	14.5	9.5 to 19.5

Haloperidol, despite being a high-potency agent, has been linked in case reports to QTc prolongation and TdP, though the frequency and magnitude of QTc prolongation is thought to be substantially less than with thioridazine and similar to that with many atypical antipsychotics. In this study, oral haloperidol prolonged the QTc interval by less than 5 msec, not reflective of its ability to cause QTc prolongation and TdP seen in the literature. When used for in-hospital agitation, intravenous (IV) haloperidol produced a dose-dependent increase in the risk of a QTc > 500 msec and the risk of TdP (Sharma et al., 1998). The higher risk of QTc prolongation and TdP with IV haloperidol may be explained in part by the fact that it is used relatively frequently in medically ill individuals, who are likely at higher risk for QTc prolongation and TdP to begin with.

Although atypical antipsychotics appear to have some risk of QTc interval prolongation, these agents have only been implicated in the development of TdP in rare case reports and FDA adverse event reports. In healthy volunteers, ziprasidone seems to cause the greatest mean QTc prolongation when compared with other SGAs, with a plateau effect at approximately 20msec. Quetiapine also seems to cause a dose-dependent, moderate increase in the QTc interval, by an average of 15–20 msec (Anonymous. Study 054, 2000). SGAs such as clozapine, olanzapine, aripiprazole, and paliperidone seem to have the least potential for significant QTc prolongation (Li et al., 2010).

6. Conclusion

Prevention of QTc prolongation with the use of antipsychotics is hard to predict, and not all patients will experience QTc prolongation. Additionally, it is difficult to assess how much of an increase in the QTc interval warrants action. Despite the known association between the prolongation of the QTc interval and dysrhythmias, researchers recognize that this link and the risk of clinical events is poorly understood. What is understood, though, is the importance to assess risk factors for QTc prolongation, and to obtain a baseline

QTc before initiating any antipsychotic agent. Also, if, for a given indication, different drugs are available, clinicians should consider the QTc prolongation tendency of each agent when making their choice. After obtaining a baseline QTc before initiation, patients should have repeated ECGs 7 days after start of therapy and when any dose changes are made. Clinicians should use their clinical judgment when determining actions taken if QTc prolongation occurs. Generally, if the QTc > 450 msec for a drug or combination of drugs, the dose should be decreased or the drug be replaced by another not known to or has less propensity to prolong the QTc interval. In the case of a QTc > 500 msec for a drug or combination of drugs, the drug should be replaced. In both cases, repeat ECGs should be performed after action has been taken, and the patient's serum electrolyte levels should be monitored carefully.

References

Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-Induced Agranulocytosis -- Incidence and Risk Factors in the United States. N Engl J Med 1993; 329:162-167

American Psychiatric Association (2000). Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition: DSM-IV-TR®. American Psychiatric Pub. ISBN 978-0-89042-025-6.

Anonymous. Study 054. Briefing document for Zeldox capsules (ziprasidone HCL). FDA psychopharmacological drugs advisory committee, July 19, 2000. http:// www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1a.pdf

Ban TA, Healy D, Shorter E. Preface. In: Ban TA, Healy D, Shorter E, editors. The rise of psychhopharmacology and the story of CINP. Budapest: Animula; 1998. pp. VII–VIII.

Ban TA. Fifty years chlorpromazine: a historical perspective. Neuropsychiatr Dis Treat 2007 August; 3(4): 495-500

Clozapine-Induced Agranulocytosis -- Incidence and Risk Factors in the United States. N Engl J Med 1993; 329:162-167

Coley KC, Carter CS, et al. Effectiveness of antipsychotic therapy in a naturalistic setting: a comparison between risperidone, perphenazine, and haloperidol. J Clin Psychiatry. 1999;60(12):850.

Crumb W, Ekins S, Sarazan R, et al. Effects of antipsychotic drugs on Ito ,INa,Isus,IK1, and hERG: QT prolongation, structure activity relationship , and network analysis. Pharm Res 2006;23:1133–43.

Harrigan EP, Miceli JJ, et al. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. J Clin Psychopharmacol. 2004 Feb;24(1):62-9.

Jose Ma. J. Alvir, Jeffrey A. Lieberman, Allan Z. Safferman, Jeffrey L. Schwimmer, and John A. Schaaf

Kahn RS, Fleischhacker WW, et al; EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet. 2008 Mar 29;371(9618):1085-97.

Kane, J; Honigfeld G, Singer J, Meltzer H (September 1988). "Clozapine for the treatment-resistant schizophrenic: a double-blind comparison versus chlorpromazine/benztropine". Archives of General Psychiatry 45 (9): 789–796

Kapur S, Remington G. Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. Biol Psychiatry. 2001;50(11):873-883.

Kudo S, Ishizaki T. Pharmacokinetics of haloperidol: an update. Clin Pharmacokinet. 1999;37(6):435.

Laborit H, Huguenard P, Alluaume R. Un noveau stabilisateur végétatif (le 4560 RP) La Presse Médicale. 1952;60:206–8.[PubMed]

Li, EC, et al. Drug-Induced QT-Interval Prolongation: Considerations for Clinicians. Pharmacotherapy 2010;30(7):684–701.

Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005 Sep 22;353(12): 1209-23.

Midha KK, McKay G, Edom R, Korchinski ED, Hawes EM, Hall K. Kinetics of oral fluphenazine disposition in humans by GC-MS. Eur J Clin Pharmacol. 1983;25(5):709.

Moss AJ, Robinson J (1992). Clinical features of the idiopathic long QT syndrome. Circulation 85 (suppl I):I140–I144.

Sanguinetti MC, Jiang C, Curran ME, Keating MT (1995). A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the Ikr potassium channel. Cell 81:299–307.

Seeman P. Atypical antipsychotics: mechanism of action. Can J Psychiatry. 2002;47(1):27.

Sharma ND, Rosman HS, Padhi ID, Tisdale JE. Torsades de pointes associated with intravenous haloperidol in critically ill patients. Am J Cardiol 1998;81:238–40.

Shen WW. A history of antipsychotic drug development. Compr Psychiatry. 1999 Nov-Dec;40(6):407-14.

Yang T, Roden DM. Extracellular potassium modulation of drug block of IKr: implications for torsade de pointes and reverse use-dependence. Circulation 1996;93:407–11.