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XXIX CICLO DI DOTTORATO IN
SCIENZE BIOMEDICHE CLINICHE E SPERIMENTALI

ECG PARAMETERS IN CHILDREN AND ADOLESCENTS TREATED WITH SECOND-GENERATION ANTIPSYCHOTICS: A 2-YEAR PROSPECTIVE STUDY

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“Start by doing what is necessary, then what is possible, and suddenly you are doing the impossible.”

St. ***Francis of Assisi***

Dedicated to those who ever believed me…

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Introduction

In the last ten years developmental disorders and its psychopharmacology have profoundly changed the approach in child and adolescent psychiatry. Research in neuroscience have focused the attention to improve diagnosis of psychiatric disorders in children and its neurobiological pathway underlying that contribute to the continuation of diseases to adulthood. The early stages of life strongly affect the development of the central nervous system and can produce persistent effects on functioning, so the purpose is to stop the negative process before the "damage" may modify neurogenic process irreparably.

To date there is no curative pharmacological intervention for psychiatric disorders in pediatrics. Most therapeutic interventions aim to reduce the most impairing symptoms of the targeted psychiatric disorders. Two main clusters of symptoms can be identified in childhood: externalizing symptoms with impulsivity, hyperactivity, and disruptive behavior and internalizing symptoms with mood and affective problems, anxiety, etc. Externalizing disorders include symptoms of ADHD, disruptive behavior, and impulsivity, as well as symptoms of tic disorder. Depressive disorders, anxiety disorders, and obsessive-compulsive disorders (OCD) are summarized as internalizing disorders (Kolch & Plener 2016). In general, pharmacotherapy of psychiatric disorders in children should be embedded in psychosocial treatment, which is recommended by many guidelines (Banaschewski et al., 2006; NICE 2005). In child psychiatry, pharmacotherapy represent a challenge: (i) treatment of a developing body and brain needs special caution; (ii) data concerning effectiveness, safety, tolerability, and long-term outcome are still scarce for many psychopharmacotherapeutic interventions within this age-group; (iii) parents often remain insecure about their treatment decision; and (iv) identifying adverse events can be challenging for caregivers and minors. To add to this, most of psychodrugs are used off-label. However, off-label use does not mean that there is no data on efficacy, effectiveness, or safety of medication in children (Kolch & Plener 2016).

Since their introduction into clinical practice, antipsychotic medications have been used in the treatment of children and adolescents with a variety of psychiatric conditions especially for externalizing symptoms (Findling et al., 2005). In recent years, the pediatric use of antipsychotics has substantially increased, due to an increment in prescription of second generation antipsychotics (SGA).

These drugs are often preferred to traditional antipsychotic drugs (AP) in reason of a better tolerability and safety profile (Briles et al., 2012; Germanò et al., 2014). The use of atypical AP in pediatric age has increased significantly in the last few years. Between 1993–1998 and 2005–2009, in the United States, visits with a prescription of antipsychotic medications per 100 persons increased from 0.24 to 1.83 for children and from 0.78 to 3.76 for adolescents (Olfson et al., 2012). The proportion of total visits including a prescription of antipsychotics increased during this period from 0.16% to 1.07% for youths (Olfson et al., 2012). Off-label use of AP which have not obtained clear pediatric indications is very common in clinical practice (Bazzano et al., 2009). However, only four drugs, such as aripiprazole, olanzapine, quetiapine, and risperidone have received FDA-approved pediatric indications, in particular for schizophrenia (age 13–17 years) and for bipolar mania (age 10–17 years; olanzapine, 13–17 years). In addition, risperidone is also indicated for irritability and aggression associated with autistic disorder (age 6–17 years), and controlled trial

data exist for disruptive behavior disorders and tic disorders (FDA, Psychopharmacologic Drugs Advisory Committee, 2009).
Moreover, the duration of treatment with these agents has been increasing (Kalverdijk et al., 2008; Rani et al., 2008). This rapid increase and the recognition that many antipsychotics induce metabolic adverse effects, thus increasing the risk for obesity, diabetes type II, and associated cardiovascular morbidity (Guo et al., 2006; Bobes et al., 2007), have raised concerns about the proper utilization of these agents and stirred controversy among both experts and the general public (Elias, 2006, Harris, 2008). After having been hailed as a safer alternative to first-generation antipsychotics because of their lower tendency to induce neurological effects, the SGA are now recognized to have a high propensity for causing other, equally problematic, adverse effects, thus triggering a reconsideration of their benefit/risk ratio, especially in children (Tyrer and Kendall, 2008; Correll, 2008a,b; Sikich et al., 2008).
The clinicians' perception that second-generation antipsychotics are safer than first-generation antipsychotics (FGA) and their expectation of better effectiveness may be one of the principal causes of the significantly increased use in the pediatric population in recent years (Vitiello et al. 2009; Zuddas et al. 2011). However, there are few safety studies of SGA in pediatric populations (Fraguas et al., 2011; Caccia et al., 2011; Arango 2014 et al., 2014; Correll et al., 2014; Alda et al., 2016).
In the past decade, various AP such as sertindole, thioridazine, and droperidol were removed from the market because of cardiac side effects (Buckley and Sanders 2000; Glassman and Bigger 2001; Fraguas et al. 2008). Other AP drugs such as ziprasidone were examined in further specific safety studies (Ziprasidone Observational Study of Cardiac Outcomes [ZODIAC Study]) (Strom et al. 2011), triggering an extensive debate regarding the cardiac safety of specific AP drugs (Fraguas et al. 2008). Various studies found an association between AP use and increase in corrected QT interval (QTc) (Buckley and Sanders 2000; Glassman and Bigger 2001).
Many AP drugs can, in various ways, prolong the QTc interval of the electrocardiogram and, in the presence of tachycardia, can provoke an increased risk of potentially lethal arrhythmias known as ''Torsade de pointes'' (Glassman and Bigger 2001; Zuddas et al. 2011).
In children and adolescents, cardiovascular side effects associated with the use of SGA and FGA include orthostatic hypotension, tachycardia, QTc prolongation, and arrhythmias (Cheng-Shannon et al. 2004; Jones et al. 2013).
In a study with a pediatric population, AP group, gender, age, smoking status, substance abuse, and diagnosis were unrelated to QTc change after introduction of the AP (de Castro et al. 2008).
In a recent meta-analysis of 55 studies with >5000 youth patients, the risk of pathological QTc prolongation seemed low during treatment with the nine AP studied in otherwise healthy young people. Nevertheless, because individual risk factors interact with medication related QTc effects, both medication and patient factors need to be considered when choosing AP treatment (Jensen et al. 2015).
Although the cardiovascular side effects during treatment with AP drugs may be less common in children and adolescents than in adults (Masi and Liboni 2011, Arango et al. 2016), the benefit of the electrocardiogram (ECG) screening is not yet clear in the pediatric population. The purpose of the study is to evaluate cardiac symptoms of SGA in a large sample of treatment-naıve (no previous AP) or quasi-naıve (AP exposure for <30 days) pediatric patients for a period of 24 months.

Chapter 1.
Atypical Antipsychotics

1.1 Definition and Mechanisms of action

From a clinical perspective, an "atypical antipsychotic" is defined in part by the "atypical" clinical properties that distinguish such drugs from conventional antipsychotics. That is, atypical antipsychotics have the clinical profile of equal positive symptom antipsychotic actions, but low extrapyramidal symptoms and less hyperprolactinemia compared to conventional antipsychotics. Thus, they are "atypical" from what is expected from a classical, conventional, first-generation antipsychotic. Since almost all of the agents with this atypical profile came after the introduction of clozapine, sometimes the atypical antipsychotics are also called second-generation antipsychotics (SGAs). From a pharmacological perspective, the current atypical antipsychotics as a class are defined as serotonin– dopamine antagonists, with simultaneous serotonin 5HT2A receptor antagonism that accompanies D2 antagonism (Figure 1) (Stahl 2013).

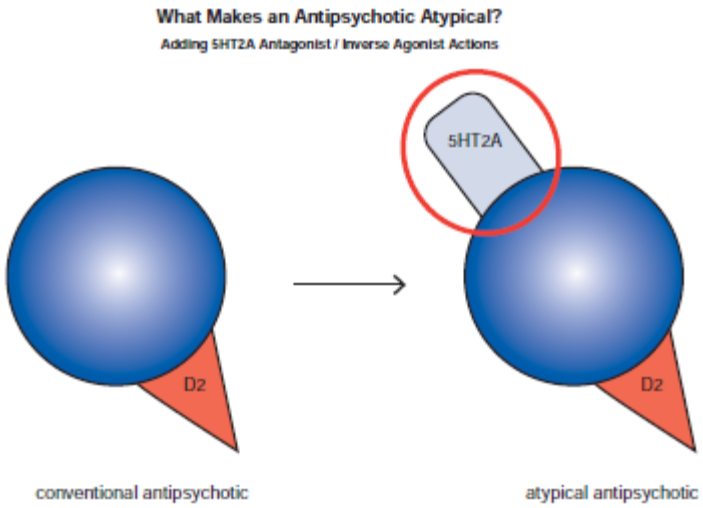

Figure 1: Serotonin–dopamine antagonist. The "atypicality" of atypical antipsychotics has often been attributed to the coupling of D2 antagonism with serotonin 5HT2A antagonism. On the right is an icon representing this dual pharmacological action. (Stahl 2013)

Pharmacologic actions in addition to 5HT2A antagonism that can hypothetically also mediate the atypical antipsychotic clinical profile of low EPS and less hyperprolactinemia with comparable antipsychotic actions include partial agonist actions at 5HT1A receptors and partial agonist actions at D2 receptors. In order to understand the mechanism of action of atypical antipsychotics and how this differs from conventional antipsychotics, it is necessary to have more detailed understanding of the neurotransmitter serotonin and its receptors.

Serotonin synthesis and termination of action

Serotonin is also known as 5-hydroxytryptamine and abbreviated as 5HT. Synthesis of 5HT begins with the amino acid tryptophan, which is transported into the brain from the plasma to serve as the 5HT precursor. Two synthetic enzymes then convert tryptophan into serotonin: firstly tryptophan hydroxylase (TRY-OH) converts tryptophan into 5-hydroxytryptophan, and then aromatic amino acid decarboxylase (AAADC) converts 5HTP into 5HT. After synthesis, 5HT is taken up into

synaptic vesicles by a vesicular monoamine transporter (VMAT2) and stored there until it is used during neurotransmission.
5HT action is terminated when it is enzymatically destroyed by monoamine oxidase (MAO), and converted into an inactive metabolite. Serotonergic neurons themselves contain MAO-B, which has low affinity for 5HT, so much of 5HT is thought to be enzymatically degraded by MAO-A outside of the neuron once 5HT is released. The 5HT neuron also has a presynaptic transport pump for serotonin called the serotonin transporter (SERT) that is unique for 5HT and that terminates serotonin's actions by pumping it out of the synapse and back into the presynaptic nerve terminal where it can be re-stored in synaptic vesicles for subsequent use in another neurotransmission (Stahl 2013).

5HT2A receptors

The key to understanding why antipsychotics are atypical is to understand the pharmacology of 5HT2A receptors, and the significance of what happens when they are blocked by atypical antipsychotics. All 5HT2A receptors are postsynaptic, and 5HT2A receptors are located in many brain regions. When they are located on cortical pyramidal neurons, they are excitatory and can thus enhance downstream glutamate release. Glutamate regulates downstream dopamine release, so stimulating or blocking 5HT2A receptors can therefore also regulate downstream dopamine release. Cortical 5HT1A receptors also regulate downstream dopamine release (Stahl 2013).

5HT2A receptors are brakes on dopamine release in the Striatum

5HT2A stimulation of cortical pyramidal neurons by serotonin hypothetically blocks downstream dopamine release in the striatum. It does this via stimulation of glutamate release in the brainstem that triggers release of inhibitory GABA there. Release of dopamine from neurons in the striatum is thus inhibited.

5HT2A antagonism cuts the brake cable

5HT2A antagonism of cortical pyramidal neurons by an atypical antipsychotic interferes with serotonin applying its braking action to dopamine release via 5HT2A receptors. Thus, 5HT2A antagonism in the cortex hypothetically stimulates downstream dopamine release in the striatum. It does this by reducing glutamate release in the brainstem, which in turn fails to trigger the release of inhibitory GABA at dopamine neurons there. Release of dopamine from neurons downstream in the striatum is thus disinhibited, which should theoretically mitigate EPS.

5HT2A receptors in other brain areas are also a brake on dopamine release in the striatum

5HT2A receptors theoretically regulate dopamine release from nigrostriatal dopamine neurons by additional mechanisms in additional brain areas. That is, serotonin neurons whose cell bodies are in the midbrain raphe may innervate nigrostriatal dopamine neurons both at the level of the dopamine neuronal cell bodies in the substantia nigra and at the dopamine neuronal axon terminals in the striatum. This innervation may be either via a direct connection between the serotonin neuron and the dopamine neuron, or via an indirect connection with a GABA interneuron. 5HT2A receptor stimulation by serotonin at either end of substantia nigra neurons hypothetically blocks dopamine release in the striatum. On the other hand, 5HT2A receptor antagonism by an atypical antipsychotic at these same sites hypothetically stimulates downstream dopamine release in the striatum. Such release of dopamine in the striatum should mitigate EPS, which is theoretically why antipsychotics with 5HT2A antagonist properties are atypical. 5HT1A receptors also regulate dopamine release in the striatum (Stahl 2013).

5HT2A receptor antagonism theoretically makes an antipsychotic atypical: low EPS

Normally, serotonin reduces dopamine release from the striatum by actions of serotonin at the various 5HT2A receptors discussed above. By contrast, an atypical antipsychotic moves two different actions, namely blocking both D2 receptors and 5HT2A receptors, one at a time. On the left, D2 receptors are blocked by the D2 antagonist actions of the atypical antipsychotic, just like a conventional antipsychotic. If this were the only action of the drug, there would be EPS if occupancy of D2 receptors reached 80% or more. This is exactly what happens with a conventional antipsychotic. However, atypical antipsychotics have a second property, namely to block 5HT2A receptors, which as discussed above have multiple mechanisms by which they increase dopamine release in the striatum. The result of this increased dopamine release is that dopamine competes with D2 receptor antagonists in the striatum, and reduces the D2 receptor binding there below 80% to more like 60%, enough to eliminate extrapyramidal symptoms. This is the hypothesis most frequently linked to the explanation for the mechanism of the most important distinguishing clinical properties of atypical antipsychotics, namely low extrapyramidal symptoms (EPS) with comparable antipsychotic actions.

5HT2A receptor antagonism theoretically makes an antipsychotic atypical: low hyperprolactinemia

Serotonin and dopamine have reciprocal roles in the regulation of prolactin secretion from the pituitary lactotroph cells. That is, dopamine inhibits prolactin release via stimulating D2 receptors, whereas serotonin promotes prolactin release via stimulating 5HT2A receptors. Thus, when D2 receptors alone are blocked by a conventional antipsychotic, dopamine can no longer inhibit prolactin release, so prolactin levels rise. However, in the case of an atypical antipsychotic, there is simultaneous inhibition of 5HT2A receptors, so serotonin can no longer stimulate prolactin release. This mitigates the hyperprolactinemia of D2 receptor blockade. Although this is interesting theoretical pharmacology in practice, not all serotonin–dopamine antagonists reduce prolactin secretion to the same extent, and others do not reduce prolactin elevations at all.

5HT2A receptor antagonism theoretically makes an antipsychotic atypical: comparable antipsychotic actions

Although a conventional antipsychotic can only decrease dopamine, and will do this at D2 receptors throughout the brain, atypical antipsychotics with their additional 5HT2A antagonist properties have much more complicated net actions on dopamine activity, since they not only decrease dopamine activity by blocking D2 receptors but they can also increase dopamine release and thus increase dopamine activity by indirectly stimulating dopamine receptors. However, these actions seem to be very different in different parts of the brain. In the nigrostriatal dopamine pathway and in the tuberoinfundibular dopamine pathway, there is sufficient dopamine release by atypical antipsychotics to reverse, in part, the unwanted actions of EPS and hyperprolactinemia. This does not appear to occur in the mesolimbic dopamine pathway, as antipsychotic actions of atypical antipsychotics are just as robust as those of conventional antipsychotics, presumably due to regional differences in the way in which 5HT2A receptors can or cannot exert control over dopamine release. The trick has been to exploit these differing regional pharmacological mechanisms to get the best clinical results by simultaneous blockade of D2 receptors and 5HT2A receptors that can fortuitously have net blockade of differing amounts of D2 receptors in different areas of the same brain at the same time with the same drug (Stahl 2013).

The making of a therapeutic window

One way to display this phenomenon of the atypical antipsychotics' differing clinical actions is to contrast what happens to dopamine D2 binding in the striatum when a pure D2 antagonist is given versus when an atypical antipsychotic that combines equal or greater potency for blocking 5HT2A receptors with D2 antagonism is given. In the case of a pure D2 antagonist like a conventional antipsychotic, the amount of D2 receptor antagonism for the striatum is assumed to be the same amount in the limbic area and in the pituitary. This is why you get EPS and hyperprolactinemia at the same dose as you get antipsychotic actions, namely when all of these D2 receptors in all of these brain areas are blocked substantially (many estimate this to be approximately 80%). There is little if any wiggle room between therapeutic actions and side effects.

However, in the case of an atypical antipsychotic, where essentially all of these drugs have an affinity for blocking 5HT2A that is equal to or greater than their affinity for blocking D2 receptors, the amount of D2 antagonism in the striatum is lowered at the same dose where the drugs have antipsychotic actions. This creates a window between the dose that exerts antipsychotic actions and the dose that causes EPS or elevated prolactin levels. While D2 receptors are assumed to be blocked by 80% in the limbic areas to cause antipsychotic actions, the D2 receptors in both the striatum and the pituitary are assumed to be blocked by only approximately 60%, below the threshold for side effects. Of course, if an atypical antipsychotic has its dose raised high enough, there will eventually be 80% blockade of even the striatum and pituitary, and the drug will lose its atypical properties. Thus, the drug is only "atypical" in the dosing window. This window is created by the fact that atypical antipsychotics almost always have higher affinity for 5HT2A receptors than they do for D2 receptors.

You can visualize the relative receptor actions of atypical antipsychotics on 5HT2A receptors versus D2 receptors by viewing simultaneously the relative potencies of the individual atypical antipsychotic drugs for binding 5HT2A receptors versus D2 receptors (Figure 2). The atypical antipsychotics can be categorized many ways, but for our discussion throughout this section, we will organize them as either the "pines" (peens) (Figure 2-A), the "dones" (Figure 2-B), or "two pips and a rip" (Figure 2-C), like suggested by Stahl's book (Stahl 2013).

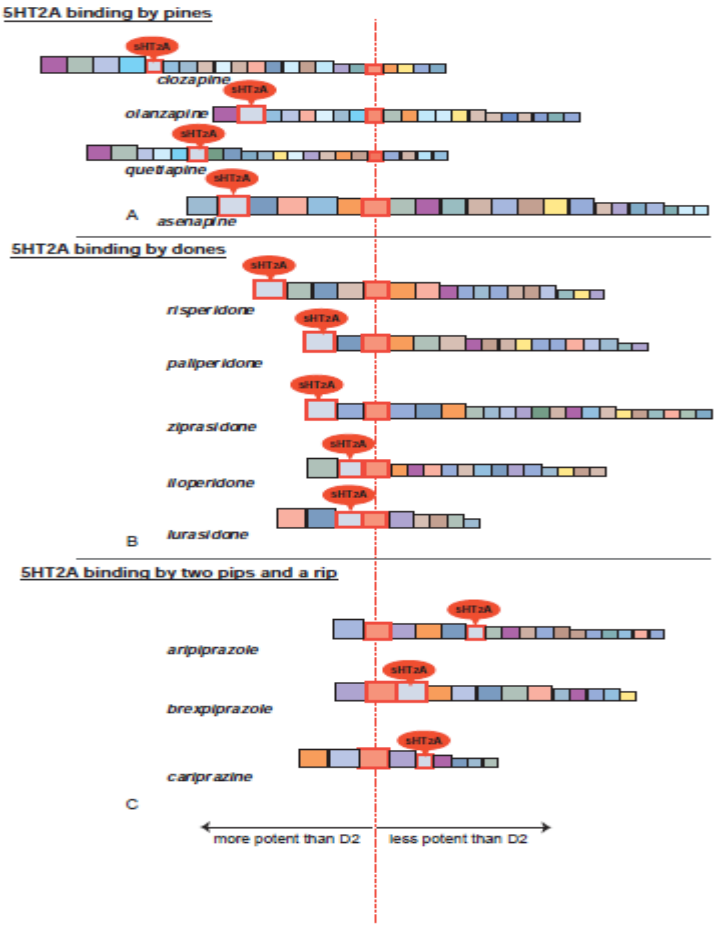

Figure 2: 5HT2A binding by atypical antipsychotics (Stahl 2013) Shown here is a visual depiction of the binding profiles of atypical antipsychotics. Each colored box represents a different binding property, with the size and positioning of the box reflecting the binding potency of the property (i.e., size indicates potency relative to a standard Ki scale, while position reflects potency relative to the other binding properties of that drug).
The vertical dotted line cuts through the dopamine 2 (D2) receptor binding box, with binding properties that are more potent than D2 on the left and those that are less potent than D2 on the right.
Interestingly, D2 binding is not the most potent property for any of the atypical antipsychotics. (A) The "pines" (clozapine, olanzapine, quetiapine, asenapine) all bind much more potently to the 5HT2A receptor than they do to the D2 receptor. (B) The "dones" (risperidone, paliperidone, ziprasidone, iloperidone, lurasidone) also bind more potently to the 5HT2A receptor than to the D2 receptor, or show similar potency at both receptors. (C) Aripiprazole and cariprazine both bind more potently to the D2 receptor than to the 5HT2A receptor, while brexpiprazole has similar potency at both receptors.

The point is that although no two atypical antipsychotics have exactly the same pharmacologic binding profiles, it is easy to see that for the pines (Figure 2) and for the dones (Figure 2), 5HT2A receptor binding is always to the left of D2 binding. This binding property of greater 5HT2A than D2 binding potency is what is widely thought to make these drugs "atypical" antipsychotics and to create the "window" of atypical antipsychotic action that is theoretically linked to low EPS as well as to low propensity to elevate prolactin.
Note that for two pips and a rip, the 5HT2A binding potency is to the right of D2 binding, and thus less potent than D2 binding (Figure 2). The fact that the two pips and a rip are still atypical antipsychotics in their clinical properties is attributed to other actions, as will be explained in the sections below on 5HT1A receptors and partial agonism of D2 receptors. Rather than having more potent 5HT2A than D2 binding, as is the case for the pines and the dones, binding at 5HT1A receptors and partial agonism of D2 receptors may account for the atypical properties of the two pips and a rip (Stahl 2013).
5HT1A partial agonism can also make an antipsychotic atypical

In order to understand how 5HT1A partial agonism can also reduce EPS, it is important to grasp how 5HT1A receptors function in various parts of the brain, and how they can regulate dopamine release in the striatum. Postsynaptic 5HT1A receptors in prefrontal cortex are accelerators for dopamine release in striatum

If 5HT2A stimulation is the "brake" stopping downstream dopamine release and 5HT2A antagonism"cuts the brake cable," enhancing dopamine release, what is the accelerator for downstream dopamine release in the striatum? The answer is postsynaptic 5HT1A receptors on pyramidal neurons in the cortex. 5HT1A receptor stimulation in the cortex hypothetically stimulates downstream dopamine release in the striatum, by reducing glutamate release in the brainstem, which in turn fails to trigger the release of inhibitory GABA at dopamine neurons there. Dopamine neurons are thus disinhibited, just as they are by a 5HT2A antagonist. This would theoretically cause dopamine release in striatum, and mitigate EPS.

Presynaptic 5HT1A receptors in raphe are also accelerators for dopamine release in the striatum

5HT1A receptors can not only be postsynaptic throughout the brain, but also they can be presynaptic on the dendrites and cell bodies of serotonin neurons in the midbrain raphe. In fact, the only type of presynaptic 5HT receptor at the somatodendritic end of a serotonin neuron is a 5HT1A receptor.

When 5HT is detected at presynaptic somatodendritic 5HT1A receptors on neuronal dendrites and on the neuronal cell body, this activates an autoreceptor function that causes a slowing of neuronal impulse flow through the serotonin neuron and a reduction of serotonin release from its axon terminal. Downregulation and desensitization of these presynaptic 5HT1A somatodendritic autoreceptors are thought to be critical to the antidepressant actions of drugs that block serotonin reuptake.

When serotonin occupies a presynaptic 5HT1A somatodendritic autoreceptor in the midbrain raphe, where they are located, this turns off serotonin neurons. The serotonin pathways from raphe to substantia nigra and to striatum are thus "off" in the presence of serotonin at presynaptic 5HT1A receptors; as a consequence, serotonin is not released onto postsynaptic 5HT2A receptors on nigrostriatal neurons, activation of which would ordinarily inhibit dopamine release in the striatum. Lack of serotonin release due to stimulation of presynaptic 5HT1A receptors thereby allows the nigrostriatal dopamine neurons to be active and thus to release dopamine in the striatum. Pre- and postsynaptic 5HT1A receptors work together to enhance dopamine release in the striatum, and when both are stimulated by certain atypical antipsychotics, this theoretically mitigates EPS.

Some, but not all, atypical antipsychotics have potent 5HT1A partial agonist properties. In particular, the two pips and a rip, namely aripiprazole and the experimental antipsychotics brexpiprazole and cariprazine, all have 5HT1A partial agonist actions not only more potent than their 5HT2A antagonist actions, but comparable to their D2 antagonist actions. The 5HT2A antagonist actions may also contribute to the atypical properties of these three agents, but the reduction of EPS for these agents is likely given a major boost by the additional presence of potent 5HT1A partial agonist actions. In addition, note that potentially clinically relevant 5HT1A partial agonist actions are present for a few of the pines (especially clozapine and quetiapine) and some of the dones (especially lurasidone, iloperidone, and ziprasidone), with those binding properties further to the left being relatively more potent and thus potentially more clinically relevant as well at antipsychotic dosing levels.

The most dopamine release in striatum and fewest EPS may come when you take your foot off the brake and also step on the accelerator If blocking 5HT2A receptors is like taking your foot off the brake, and if stimulating 5HT1A receptors is like stepping on the accelerator, this could account for why both of these actions that release dopamine from the striatum might be additive. It may also potentially explain why atypical antipsychotics with either potent 5HT2A antagonism or potent 5HT1A agonist/partial agonist properties, or with both actions, have a reduced incidence of EPS. Thus, either pharmacologic action alone or both pharmacologic actions together seem to contribute to the atypical antipsychotic profiles of specific atypical antipsychotic drugs (Stahl 2013).
Not only do several atypical antipsychotics have 5HT1A partial agonist actions, but so do various agents with known or suspected antidepressant actions, from vilazodone to buspirone (augmentation of selective serotonin reuptake inhibitors [SSRIs]/serotonin–norepinephrine reuptake inhibitors [SNRIs]), to experimental agents with selective or mixed 5HT1A partial agonism (e.g., vortioxetine).
This has led to speculation that those atypical antipsychotics with 5HT1A partial agonist actions that are proven antidepressants (such as quetiapine and aripiprazole) may be working in part through this mechanism, and that other atypical antipsychotics with 5HT1A partial agonist actions are also potential antidepressants (such as brexpiprazole, cariprazine, lurasidone, iloperidone, and others). The mechanism of how 5HT1A partial agonism exerts its possible antidepressant efficacy is unknown, but could be linked to release of dopamine and norepinephrine in prefrontal cortex or to the potentiation of serotonin levels in the presence of a serotonin reuptake inhibitor, which would be theoretically linked to antidepressant actions.

5HT1B/D receptors

Presynaptic 5HTreceptors are autoreceptors, and detect the presence of 5HT, causing a shutdown of further 5HT release and 5HT neuronal impulse flow. Discussed above are the 5HT1A presynaptic receptors at the somatodendritic end of the serotonin neuron.
There is also another type of presynaptic serotonin receptor, and it is located at the other end of the neuron, on the axon terminals. When 5HT is detected in the synapse by presynaptic 5HT receptors on axon terminals, it occurs via a 5HT1B/D receptor which is also called a terminal autoreceptor . In the case of the 5HT1B/D terminal autoreceptor, 5HT occupancy of this receptor causes a blockade of 5HT release. On the other hand, drugs that block the 5HT1B/D autoreceptor can promote 5HT release, and this could hypothetically result in antidepressant actions, as for the experimental antidepressant vortioxetine. Among the atypical antipsychotics, only iloperidone, ziprasidone and asenapine , unproven yet as antidepressants, have 5HT1B/D binding more potent than or comparably potent to D2 binding, although many other agents have low potency at this receptor, including the proven antidepressants olanzapine, quetiapine, and aripiprazole. However, the link of 5HT1B/D to the antidepressant actions of these agents, although plausible, remains unproven.

5HT2C receptors

5HT2C receptors are postsynaptic, and regulate both dopamine and norepinephrine release. Stimulation of 5HT2C receptors is one experimental approach to a novel antipsychotic, since this suppresses dopamine release, curiously more from the mesolimbic than from the nigrostriatal pathways, yielding an excellent preclinical profile: namely, an antipsychotic without EPS. One such agent, the 5HT2C selective agonist vabacaserin, has entered clinical trials for the treatment of schizophrenia. Stimulating 5HT2C receptors is also an experimental approach to the treatment of

obesity, since this leads to weight loss in both preclinical and clinical studies. Another 5HT2C selective agonist, lorcaserin, is now approved for the treatment of obesity. Blocking 5HT2C receptors stimulates dopamine and norepinephrine release in prefrontal cortex, and has pro-cognitive but particularly antidepressant actions in experimental animals. Several known and experimental antidepressants are 5HT2C antagonists, ranging from certain tricyclic antidepressants to mirtazapine, to agomelatine, and some of the dones (especially lurasidone, iloperidone, and ziprasidone) with those binding properties further to the left being relatively more potent and thus potentially more clinically relevant as well at antipsychotic dosing levels.

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Presynaptic 5HTreceptors are autoreceptors, and detect the presence of 5HT, causing a shutdown of further 5HT release and 5HT neuronal impulse flow. There is also another type of presynaptic serotonin receptor, and it is located at the other end of the neuron, on the axon terminals. When 5HT is detected in the synapse by presynaptic 5HT receptors on axon terminals, it occurs via a 5HT1B/D receptor which is also called a terminal autoreceptor. In the case of the 5HT1B/D terminal autoreceptor, 5HT occupancy of this receptor causes a blockade of 5HT release. On the other hand, drugs that block the 5HT1B/D autoreceptor can promote 5HT release, and this could hypothetically result in antidepressant actions, as for the experimental antidepressant vortioxetine. Among the atypical antipsychotics, only iloperidone, ziprasidone and asenapine, unproven yet as antidepressants, have 5HT1B/D binding more potent than or comparably potent to D2 binding, although many other agents have low potency at this receptor, including the proven antidepressants olanzapine, quetiapine, and aripiprazole. However, the link of 5HT1B/D to the antidepressant actions of these agents, although probable, remains unproven.

5HT2C receptors

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Stimulating 5HT2C receptors is also an experimental approach to the treatment of obesity, since this leads to weight loss in both preclinical and clinical studies. Another 5HT2C selective agonist, lorcaserin, is now approved for the treatment of obesity. Blocking 5HT2C receptors stimulates dopamine and norepinephrine release in prefrontal cortex, and has pro-cognitive but particularly antidepressant actions in experimental animals. It is also plausible but unproven that 5HT7 antagonism could contribute to the known antidepressant actions of aripiprazole, especially in combination with SSRIs/SNRIs and in combination with its 5HT1A partial agonism. This leads to speculation that lurasidone, asenapine, brexpiprazole, and others could have antidepressant potential in unipolar major depressive disorder, especially in combination with SSRIs/SNRIs, but more clinical trials are necessary at this time to prove this. Recent data already indicate antidepressant actions of lurasidone in bipolar depression.

<u>D2 partial agonism (DPA) makes an antipsychotic atypical</u>

Some antipsychotics act to stabilize dopamine neurotransmission in a state between silent antagonism and full stimulation/agonist action by acting as partial agonists at D2 receptors (Figure 3) (Stahl 2013).

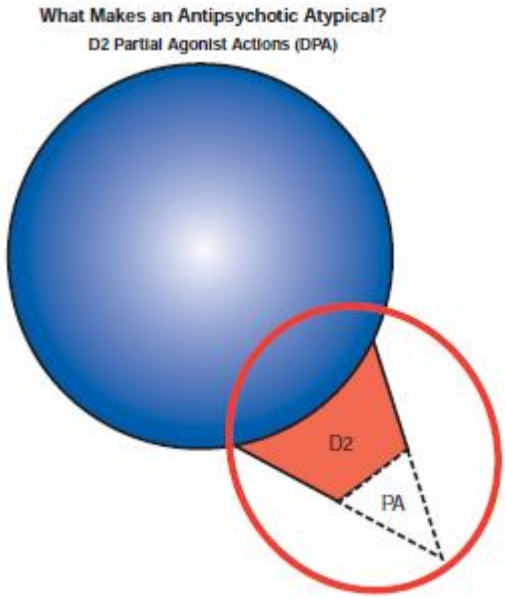

Figure 3: D2 partial agonism (Stahl 2013). A third property that may render an antipsychotic atypical is that of dopamine 2 partial agonism (DPA). These agents may stabilize dopamine neurotransmission in a state between silent antagonism and full stimulation.

Dopamine partial agonists (DPAs) theoretically bind to the D2 receptor in a manner that is neither too antagonizing like a conventional antipsychotic ("too cold," with antipsychotic actions but extrapyramidal symptoms), nor too stimulating like a stimulant or dopamine itself ("too hot," with positive symptoms of psychosis). Instead, a partial agonist binds in an intermediary manner ("just right," with antipsychotic actions but no extrapyramidal symptoms. For this reason, partial agonists

are sometimes called “Goldilocks” drugs if they get the balance “just right” between full agonism and complete antagonism (Figure 4).

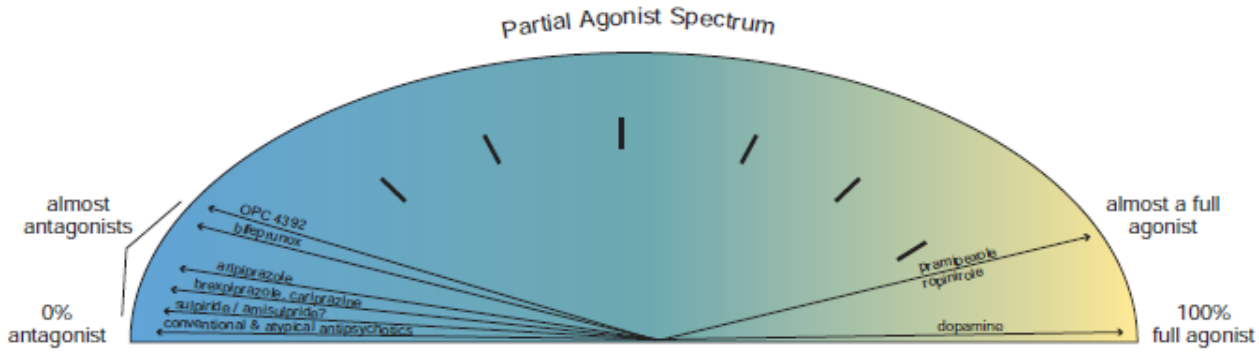

Figure 4: Spectrum of dopamine partial agonists (Stahl 2013). Dopamine partial agonists may themselves fall along a spectrum, with some having actions closer to a silent antagonist and others having actions closer to a full agonist. Agents with too much agonism may be psychotomimetic and thus not effective antipsychotics. Instead, partial agonists that are closer to the antagonist end of the spectrum (such as aripiprazole, cariprazine, or brexpiprazole, but not bifeprunox) seem to have favorable profiles. Amisulpride and sulpiride may be very partial agonists, with their partial agonist clinical properties more evident at lower doses.

However, as we shall see, this explanation is an oversimplification and the balance is different for each drug in the D2 partial agonist class. Partial agonists have the intrinsic ability to bind receptors in a manner that causes signal transduction from the receptor to be intermediate between full output and no output. The naturally occurring neurotransmitter generally functions as a full agonist, and causes maximum signal transduction from the receptor it occupies whereas antagonists essentially shut down all output from the receptor they occupy and make them “silent” in terms of communicating with downstream signal transduction cascades.

Partial agonists cause receptor output that is more than the silent antagonist, but less than the full agonist. Thus, many degrees of partial agonism are possible between these two extremes. Full agonists, antagonists, and partial agonists may cause different changes in receptor conformation that lead to a corresponding range of signal transduction output from the receptor.

An amazing characteristic of D2 receptors is that it only takes a very small amount of signal transduction through D2 receptors in the striatum for a dopamine D2 receptor partial agonist to avoid extrapyramidal side effects. Thus a very slight degree of partial agonist property, sometimes called “intrinsic activity,” can have a very different set of clinical consequences compared to a fully silent and completely blocked D2 receptor, which is what almost all known conventional and atypical antipsychotics do. Partial agonists capable of treating schizophrenia lie far to the left on the D2 partial agonist spectrum, but not all the way to full antagonist. By contrast, dopamine itself, the naturally occurring full agonist, is all the way to the right on the D2 partial agonist spectrum (Figure 4). Agents capable of treating Parkinson’s disease (such as ropinirole and pramipexole) lie far to the right on the D2 partial agonist spectrum (Stahl 2013).

What is so interesting is how very small movements off the far left and up the partial agonist spectrum can have profound effects upon the clinical properties of an antipsychotic: just slightly too close to a pure antagonist (too far to the left), and it is just a conventional antipsychotic with EPS and akathisia unless it has other 5HT2A/5HT1A properties that compensate for being too far to the left. On the other hand, just slightly too far to the right, and it is an atypical antipsychotic without EPS or akathisia, but one that is too activating, capable of worsening positive symptoms of schizophrenia and also causing intolerable nausea and vomiting (comparable to “too hot”). The elusive Goldilocks solution of a drug that is a tolerable high-dose antipsychotic without EPS and a

tolerable low-dose antidepressant is being sought empirically by iterative introduction of a series of partial agonists each differing in their intrinsic activity that demonstrate the consequences of being either too close to the antagonist end of the spectrum, or too far off that end of the spectrum. This is just a theory of how building tiny bits of partial agonism into a D2 antagonist can dramatically change its clinical properties, but there is some reasonable evidence for this possibility, given that there are several agents with significant clinical testing or experience that are available and that have tested this pharmacological concept in patients with schizophrenia.

For example, it is possible that the older agents sulpiride and amisulpride (not available in the US) are just barely off the antagonist part of the spectrum, without sufficient 5HT2A or 5HT1A actions to forgive this, and thus have low but not zero EPS with robust antipsychotic activities at high doses, plus anecdotal but not well-tested antidepressant and negative symptom clinical actions at low doses (Stahl 2013).

The first dart thrown at the partial agonist spectrum was OPC4392 (structurally and pharmacologically related to both aripiprazole and brexpiprazole, which were tested later). OPC4392 landed too close to the agonist part of the curve, although it had relatively little intrinsic activity. This surprised investigators, who discovered that although OPC4392 improved negative symptoms of schizophrenia, it also activated rather than consistently improved positive symptoms of schizophrenia, and in balance did not have the profile of an acceptable antipsychotic so was never marketed (Stahl 2013).

Two more agents with antagonist actions greater than aripiprazole are in late-stage clinical testing, namely a second "pip," brexpiprazole, and the "rip" cariprazine. So far, both appear to have efficacy in schizophrenia, and clinical trials and dose finding in mania and depression are ongoing, but both agents, although having subtle pharmacologic differences, are looking as though they will have significant clinical differences not only from aripiprazole but also from each other. The take-away point here is that D2 partial agonism can make an antipsychotic atypical, and that subtle changes in the degree of intrinsic efficacy along the partial agonist scale at the full antagonist end of the spectrum can have profound clinical consequences. Of course, we have to wait quite long to show efficacy and later on safety in pediatric populations.

1.2 Clinical Actions

Although D2 antagonist/partial agonist properties can explain the antipsychotic efficacy for positive symptoms as well as many side effects of antipsychotics, and the 5HT2A antagonist, 5HT1A partial agonist and muscarinic antagonist properties can explain the reduced propensity for EPS or elevating prolactin of various antipsychotics, there are many additional pharmacologic properties of these drugs. In fact, the atypical antipsychotics as a class have perhaps the most complicated pattern of binding to neurotransmitter receptors of any drug class in psychopharmacology, and no two agents have an identical portfolio of these additional properties. Binding properties of some individual atypical antipsychotic are discussed later in the next section. In this part, we will review a number of other receptor interactions for the class of atypical antipsychotic drugs in general, and show where the potential links may exist between pharmacology and clinical actions. Although many of the actions of these drugs on the various receptors are fairly well established, the link

between receptor binding and clinical actions remains hypothetical, with some links better established than others.

a. Antidepressant actions in bipolar and unipolar depression

Atypical antipsychotics are really misnamed, because they also have antidepressant actions alone and in combination with other antidepressants. It does not seem likely that D2 antagonism or 5HT2A antagonism are the mechanisms for this, because agents with only those properties are not effective antidepressants, and antipsychotics with these properties often work at doses lower than those necessary for antipsychotic actions, perhaps due to other pharmacologic actions. The actions hypothetically linked to antidepressant effects are those that exist for proven antidepressants, although not every atypical antipsychotic with a potential antidepressant mechanism is proven to be an antidepressant in clinical trials. Numerous receptor binding properties linked to various serotonin receptors have already been mentioned, including 5HT1A partial agonist actions and antagonism of 5HT1B/D, 5HT2C, 5HT3, and 5HT7 receptors. Additional mechanisms linked to antidepressant actions that are shared by various atypical antipsychotics include:

1) Serotonin and/or norepinephrine reuptake inhibition – Only quetiapine has potency greater than its D2 binding, but ziprasidone and zotepine have weak binding at these sites.

2) Alpha-2 (α2) antagonism – The proven antidepressant mirtazapine is best known for α2 antagonism, but several atypical antipsychotics also have this action with variable degrees of potency, including essentially all the pines (higher potency especially for quetiapine and clozapine) and dones (higher potency especially for risperidone as well as aripiprazole.

b. Antimanic actions

All antipsychotics are effective for psychotic mania, but atypical antipsychotics appear to have greater efficacy, or at least greater documentation of efficacy, for nonpsychotic mania, leading to the major hypothesis that it is the D2 antagonism/partial agonism combined with 5HT2A antagonism that is the mechanism of this. However, proven for aripiprazole and with preliminary evidence of efficacy for cariprazine, agents with D2 partial agonism and with 5HT1A partial agonism more potent than 5HT2A antagonism are also effective for mania, so 5HT1A agonist/partial agonist actions may contribute to antimanic efficacy as well.

c. Anxiolytic actions

A somewhat controversial use of atypical antipsychotics is for the treatment of various anxiety disorders. Some studies suggest efficacy of various atypical antipsychotics for generalized anxiety disorder, and to augment other agents for other anxiety disorders, but perhaps more controversial is their use for posttraumatic stress disorder (PTSD). Furthermore, side effects and cost considerations and the lack of regulatory approval have tended to restrict this application of the atypical antipsychotics. It is possible that the antihistamine and anticholinergic sedative properties of some of these agents are calming in some patients and responsible for anxiolytic action in them. Agents with these properties are listed in the following section on sedation. Anecdotal use as well as clinical evidence for utility in various anxiety disorders is probably greatest for quetiapine.

d. Sedative-hypnotic and sedating actions

There has been a longstanding debate as to whether sedation is a good or a bad property for an antipsychotic. The answer seems to be that sedation is both good and bad. In some cases, particularly for short term treatment, sedation is a desired therapeutic effect, especially early in treatment, during hospitalization, and when patients are aggressive, agitated, or needing sleep induction. In other cases, particularly for long-term treatment, sedation is generally a side effect to be avoided because diminished arousal, sedation, and somnolence can lead to cognitive impairment. When cognition is impaired, functional outcomes are compromised. Blocking one or more of three particular receptors is held theoretically responsible for causing sedation: M1-muscarinic cholinergic receptors, H1-histaminic receptors, and α1-adrenergic receptors. Blocking central α1-adrenergic receptors is associated with sedation, and blocking peripheral α1-adrenergic receptors is associated with orthostatic hypotension. Central dopamine, acetylcholine, histamine, and norepinephrine are all involved in arousal pathways so it is not surprising that blocking one or more of these systems can lead to sedation as well as to cognitive problems. Pharmacologicevidence suggests that the best long-term outcomes in schizophrenia result when adequate D2/5HT2A/5HT1A receptor occupancy improves positive symptoms of psychosis, rather than from nonspecific sedation resulting from muscarinic, histaminic, and adrenergic receptor blockade. All atypical antipsychotics are not equally sedating because they do not all have potent antagonist properties at H1 histamine, muscarinic cholinergic, and α1-adrenergic receptors.
Obviously drugs that combine potent actions at all three receptors will be the most sedating:
Potent antihistamine actions – Clozapine, quetiapine, olanzapine, and iloperidone are alletical antidepressant actions of one or more of the atypical antipsychotics are shown in literature, and more potent H1 antagonists than D2 antagonists. All other antipsychotics have moderate potency, except lurasidone, which has essentially no binding to H1.
Potent anticholinergic actions – Only the pines clozapine, quetiapine, and olanzapine have high potency for muscarinic receptors, whereas there is essentially no muscarinic cholinergic receptor binding for the other atypical antipsychotics, including asenapine.
Potent α1-adrenergic antagonism – All atypical antipsychotics have at leastmoderate binding potency to α1-adrenergic receptors, but the most potent relative to their D2 binding are clozapine, quetiapine, risperidone, and iloperidone.

Given this portfolio of findings, it is not surprising that in general the pines are more sedating than the dones, and furthermore, the presence of antihistamine and antimuscarinic binding has implications for how fast one can taper and switch these agents. Alpha-1 antagonist properties may have theoretical implications for lowering EPS by a novel mechanism.

1.3 Principles Atypical Antipsychotics

Here we will review some of the differences among 6 selected antipsychotic agents of the AAPs prescribed in child and adolescent psychiatry.
The pharmacologic properties represented in the icons shown in the next section are conceptual and not precisely quantitative and are shown in two ways: a rank order of binding potencies in a strip below an icon containing the most important binding properties.

As before, more potent binding is shown to the left of the value for the D2 receptor, less potent binding is shown to the right. As mentioned earlier, these agents are all dosed to treat psychosis in order to occupy about 60% or more of D2 receptors. Thus, all receptors to the left of D2 are occupied at the level of 60% or more at antipsychotic dosing levels. For those receptors to the left of D2, there are also potentially clinically relevant receptor actions even at doses below those for treating psychosis. The receptors to the right of D2 are occupied at a level of less than 60% at antipsychotic dosing levels. Those that are within an order of magnitude of potency of D2 are shown to the right of D2, and have potentially relevant clinical action despite lower levels of occupancy than D2 receptors, with declining occupancy levels as the receptor is listed further to the right, and also at lower than antipsychotic dosing levels (Stahl 2013). The point is really that no two atypical antipsychotics have exactly the same pharmacologic binding profiles, even though many of their properties overlap. The distinctive pharmacologic properties of each atypical antipsychotic are worth noting in order to match the best antipsychotic agent to each individual patient.

1.3.1 Clozapine

Clozapine is considered to be the prototype of the atypical antipsychotics, as it was the first to be recognized as having few if any extrapyramidal side effects, not causing tardive dyskinesia, and not elevating prolactin. Clozapine is one of five antipsychotics with somewhat related chemical structures. Although certainly a serotonin 2A—dopamine 2 antagonist, clozapine also has one of the most complex pharmacologic profiles in psychopharmacology, let alone among the atypical antipsychotics (Figure 5).

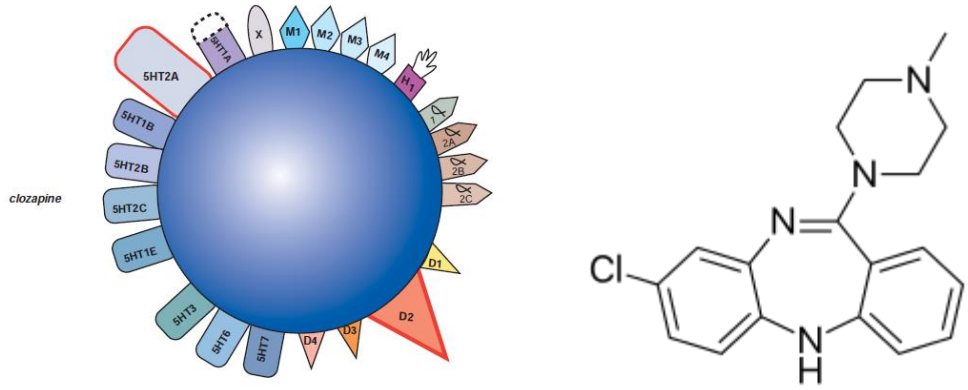

Figure 5: Clozapine's pharmacological profile (Stahl 2013) and chemical structure.

Clozapine is the one atypical antipsychotic recognized as particularly effective when conventional antipsychotic agents have failed. Although patients may occasionally experience an "awakening" (in the Oliver Sachs sense), characterized by return to a near normal level of cognitive, interpersonal, and vocational functioning and not just significant improvement in positive symptoms of psychosis, this is unfortunately quite rare. The fact that it can be observed at all, however, gives hope to the possibility that a state of wellness might some day be achieved in schizophrenia by the right mix of pharmacologic mechanisms. Such awakenings have been observed on rare occasions in association with treatment with other atypical antipsychotics as well, but rarely if ever in association with conventional antipsychotic treatment.
Clozapine is also the only antipsychotic drug associated with the risk of a lifethreatening and occasionally fatal complication called agranulocytosis which occurs in 0,5 to 2% of patients.

Because of this, patients must have their blood counts monitored weekly for the first 6 months of treatment and then every 2 weeks for as long as they are treated. Clozapine also entails an increased risk of seizures, especially at high doses. It can be very sedating and is associated with the greatest degree of weight gain among the antipsychotics. Thus, clozapine may have the greatest efficacy but the most side effects among the atypical antipsychotics.

Pharmacologists have been attempting to define what it is about clozapine's biochemical mechanism of action that accounts for its special efficacy as well as its side effects. As discussed extensively in this chapter, SDA properties may account in part for reducing EPS, for reducing tardive dyskinesia, and perhaps even for lack of prolactin elevation; SDA properties may even help explain improvement in negative symptoms of schizophrenia. However, the concept of SDA does not appear to explain the therapeutic actions of clozapine in treatment-resistant cases because clozapine is superior to other agents that share this property.

Serotonin-dopamine antagonist properties also do not explain clozapine's side effects of weight gain, sedation, seizures, and agranulocytosis. The mechanism of clozapine's induction of agranulocytosis remains unclear, but fortunately no other atypical antipsychotic drug appears to share this problem. Seizures are also poorly understood but are not a serious problem for any other atypical antipsychotic.

Weight gain, most notorious for clozapine among all of the atypical antipsychotics, appears to correlate best with its antihistaminic binding properties, perhaps made worst by concomitant serotonin 2C antagonist actions. Sedation may be linked to antihistaminic and anticholinergic actions.

In view of the risk/benefit ratio for clozapine, this agent is not generally considered a first-line agent for the treatment of psychosis but one to consider when several other agents have failed. It is especially useful in quelling violence and aggression in difficult patients, may reduce suicide rates in schizophrenia, and may reduce tardive dyskinesia severity, especially over long treatment intervals.

1.3.2 Risperidone

This agent is a “done” and thus has a different chemical structure and a different pharmacologic profile than the “pines” (Figure 2-A; Figure 6). Risperidone has atypical antipsychotic properties especially at lower doses, but can become more “conventional” at high doses in that EPS can occur if the dose is too high. Risperidone thus has favored uses in schizophrenia and bipolar mania at moderate doses, but also for other conditions where lower or moderate doses of antipsychotics can be used, such as for children and adolescents with psychotic disorders.

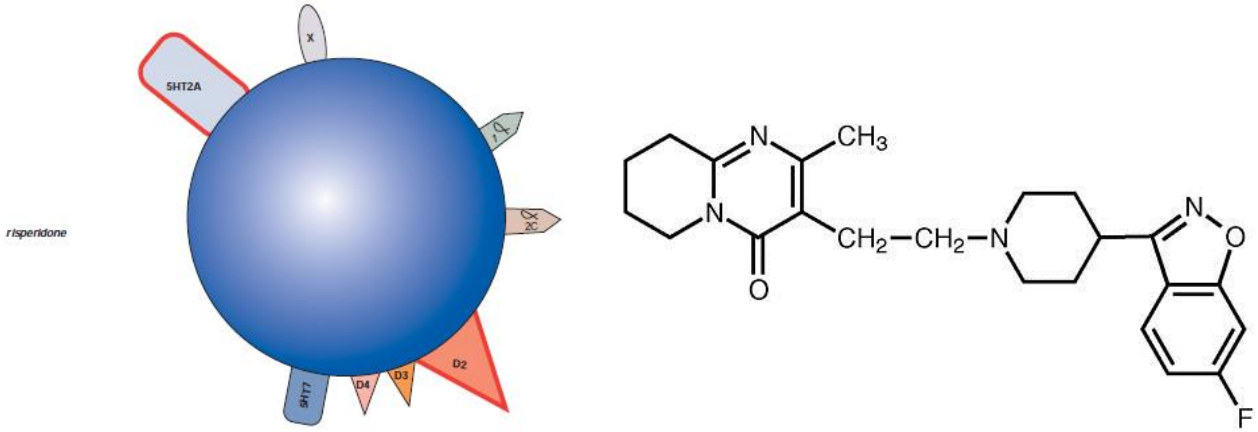

Figure 6: Risperidone's pharmacological profile (Stahl 2013) and chemical structure.

Risperidone is approved for treatment of irritability associated with autistic disorder in children and adolescents (ages 5–16), including symptoms of aggression towards others, deliberate self-injury, tantrums, and quickly changing moods, for bipolar disorder (ages 10–17), and for schizophrenia (ages 13–17). Low-dose risperidone is occasionally used "off-label" for the controversial – due to a "black box" safety warning – treatment of agitation and psychosis associated with dementia. This occurs despite the fact that elderly patients with dementia related psychosis treated with any atypical antipsychotic are at increased risk of death compared to placebo, even though that overall risk is low. Obviously, the risks versus benefits must be weighed for each patient carefully prior to prescribing an atypical antipsychotic for any use. Risperidone is available in a long-term depot injectable formulation lasting for 2 weeks. Such dosage formulations may improve treatment adherence, and if adherence is enhanced may lead to better long-term outcomes. There are also an orally disintegrating tablet and liquid formulation of risperidone. Although "atypical" in terms of reduced EPS at lower doses, risperidone does raise prolactin levels even at low doses. Risperidone has a moderate amount of risk for weight gain and dyslipidemia. Weight gain can be particularly a problem in children.

1.3.3 Olanzapine

Although this agent has a chemical structure related to clozapine and is also an antagonist at both serotonin 5HT2A and dopamine D2 receptors (Figure 7), olanzapine is more potent than clozapine, and has several differentiating pharmacologic and clinical features. Olanzapine is "atypical" in that it generally lacks EPS not only at moderate antipsychotic doses, but usually even at higher antipsychotic doses. Olanzapine lacks the extreme sedating properties of clozapine, but can be somewhat sedating in some patients, as it does have antagonist properties at M1-muscarinic, H1-histaminic, and α1-adrenergic receptors. Olanzapine does not often raise prolactin levels with long-term treatment. Olanzapine is consistently associated with weight gain, perhaps because of its antihistaminic and 5HT2C antagonist properties (Stahl 2013). It ranks among the antipsychotics with the greatest known cardiometabolic risks, as it robustly increases fasting triglyceride levels and increases insulin resistance by an unknown pharmacologic mechanism postulated to be active for some atypical antipsychotics in at least some patients (Stahl 2013).

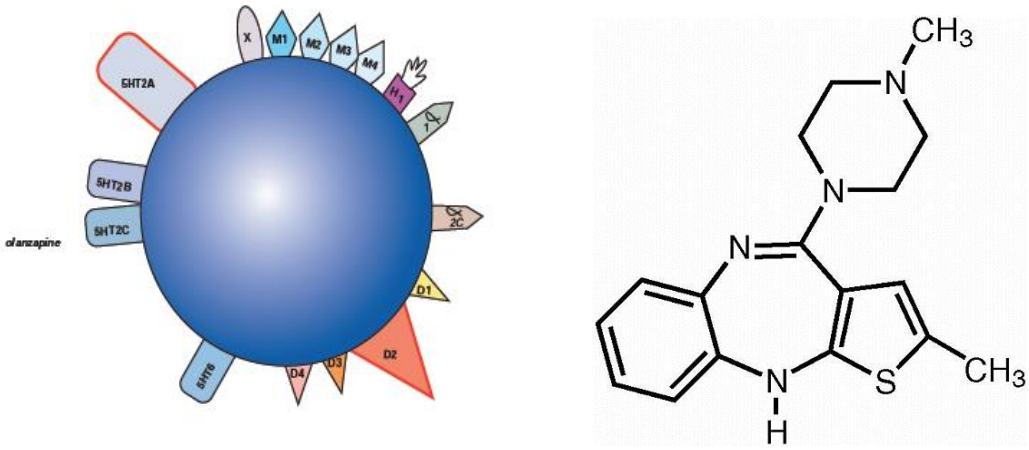

Figure 7: Olanzapine's pharmacological profile (Stahl 2013) and chemical structure.

Olanzapine tends to be used in most patients in clinical practice in higher doses (> 15 mg/day) than originally studied and approved for marketing (10– 15 mg/day), since there is the sense that higher doses might be associated not only with greater efficacy (i.e., improvement of clinical symptoms) but also with greater effectiveness (i.e., clinical outcome based upon the balance of safety and efficacy), especially in institutional settings where the dose can exceed 40 mg/day off-label. Olanzapine improves mood not only in schizophrenia but also in bipolar disorder and in treatment-resistant depression, particularly when combined with antidepressants such as fluoxetine. Perhaps the 5HT2C antagonist properties, with the weaker 5HT7 and α2 antagonist properties of olanzapine (Figures 7), especially when combined with the 5HT2C antagonist properties of the antidepressant fluoxetine, may explain some aspects of olanzapine's apparent efficacy for mood symptoms.
For patients with significant weight gain or who develop significant cardiometabolic risks, such as dyslipidemia (elevated fasting triglycerides) or diabetes, olanzapine may be considered a second-line agent.
Olanzapine can, however, be considered an appropriate choice for patients when agents with lower propensity for weight gain or cardiometabolic disturbances fail to achieve sufficient efficacy, as olanzapine can often have greater efficacy than some other agents in some patients, particularly at higher doses and for patients seen in institutional settings. The decision to use any atypical antipsychotic requires monitoring not only of efficacy but also of risks, including cardiometabolic risks, and is a tradeoff between risks and benefits that must be determined for each individual patient and for each individual drug. Olanzapine is available as an oral disintegrating tablet, as an acute intramuscular injection, and as a long-acting 4-week intramuscular depot.

1.3.4 Quetiapine

Quetiapine also has a chemical structure related to clozapine, and is an antagonist at both serotonin 5HT2A and dopamine D2 receptors, but has several differentiating pharmacologic properties, especially at different doses and with different oral formulations (Figure 8). The net pharmacologic actions of quetiapine are actually due to the combined pharmacologic actions not only of quetiapine itself but also of its active metabolite, norquetiapine. Norquetiapine has unique pharmacologic

properties compared to quetiapine, especially norepinephrine transporter(NET) inhibition (i.e., norepinephrine reuptake inhibition), but also 5HT7, 5HT2C, and α2 antagonism as well as 5HT1A partial agonist actions, all of which may contribute to quetiapine's overall clinical profile, especially its robust antidepressant effects (Figure 8).
Quetiapine has an overall very complex set of binding properties to numerous neurotransmitter receptors, many of which have higher potency than to the D2 receptor, and this may account for why this drug appears to be far more than simply an antipsychotic (Stahl 2013).

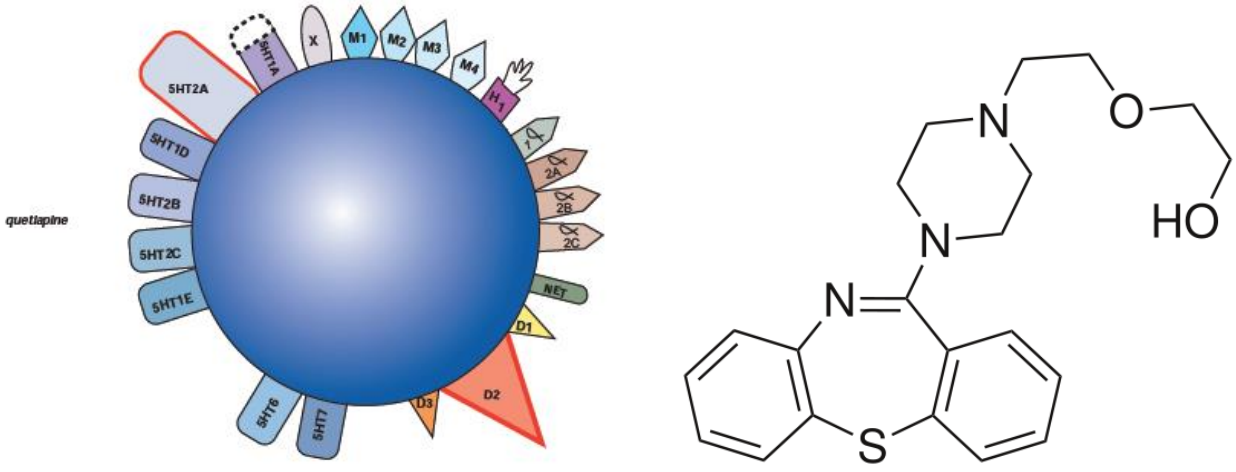

Figure 8: Quetiapine's pharmacological profile (Stahl 2013) and chemical structure.

Quetiapine is a very interesting agent, since it acts like several different drugs, depending upon the dose and the formulation. Quetiapine comes in an immediate-release (IR) formulation and in an extended-release (XR) formulation. The IR formulation has a relatively rapid onset and short duration of action, although most patients only need to take it once a day, and they usually take it at night because quetiapine is most sedating at its peak delivery shortly after taking it, due in large part to its antihistamine properties. In some ways, this makes an ideal hypnotic but not an ideal antipsychotic.
At 300 mg per day, probably the lowest effective antipsychotic dose for adults, quetiapine IR rapidly occupies more than 60% of D2 receptors, sufficient for antipsychotic action, but then quickly falls below 60% D2 receptor occupancy. This means that the antipsychotic effect may wear off after a few hours, or require dosing more than once daily or very high doses to sustain adequate D2 receptor occupancy above 60% for a full day, as its plasma drug levels fall off rapidly. By contrast, at 300 mg per day, the XR formulation of quetiapine more slowly hits its peak, yet has a rapid enough onset of 60% D2 occupancy to be effective without the same amount of sedation as quetiapine IR, and its duration of action above the 60% threshold is several hours longer than quetiapine IR. At the maximum dose of quetiapine generally used except for treatment-resistant cases, 800 mg of quetiapine IR still only occupies D2 receptors for about 12 hours above the 60% threshold, risking breakthrough symptoms at the end of the day, but quetiapine XR maintains fully effective D2 occupancy until the next dose 24 hours later. The XR formulation is thus ideal for an antipsychotic, with less peak-dose sedation but duration of action lasting all day; however, the XR formulation is not ideal for a hypnotic, because the peak is much delayed from the time when the patient takes the pill, delaying sleep onset, with a good deal of residual drug present when the patient wakes up, increasing the chances of causing hangover effects (Stahl 2013).

Although developed as an antipsychotic, quetiapine was anecdotally observed to have antidepressant effects in bipolar and unipolar depressed patients, beyond helping them sleep, and in the absence of psychotic symptoms. Over time, clinical trials have repeatedly demonstrated that in the 300 mg range, quetiapine has some of the most robust antidepressant effects of any agent in bipolar depression. At first, this did not make any sense pharmacologically for a 5HT2A–D2 antagonist with antihistaminic properties, but then the active metabolite norquetiapine was discovered with its norepinephrine reuptake blocking and 5HT2C antagonist properties, much greater than for the parent quetiapine itself. These two mechanisms can individually increase the release of both dopamine and norepinephrine, and together appear to have synergistic actions at doses below those that cause 60% D2 occupancy. In addition, quetiapine has 5HT1A partial agonist, 5HT7, α2, and 5HT1B/D antagonist properties, also theoretically linked to antidepressant actions.

Quetiapine is approved both for bipolar depression and as an augmenting agent to SSRIs/SNRIs in unipolar depression that fails to respond sufficiently to SSRI/SNRI monotherapy. Thus, the combination of quetiapine with these other antidepressants in unipolar treatment-resistant depression would have the triple monoamine actions of increasing serotonin (via SSRI/SNRI actions), dopamine, and norepinephrine (the latter two neurotransmitters theoretically via quetiapine/norquetiapine 5HT2C antagonist actions plus both quetiapine and SNRI prefrontal cortex NET blockade), while simultaneously treating symptoms of insomnia and anxiety by antihistaminic action. No matter what the dose or the formulation, quetiapine is “very atypical” in that it causes virtually no EPS at any dose, nor prolactin elevations. Thus, quetiapine tends to be a preferred atypical antipsychotic for patients with Parkinson’s disease who require treatment for psychosis (as is clozapine). Quetiapine can cause weight gain, particularly when given in moderate to high doses, as it blocks histamine 1 receptors; the 5HT2C antagonist actions of its active metabolite norquetiapine may contribute to weight gain at moderate to high doses of quetiapine (Stahl 2013). Quetiapine can increase fasting triglyceride levels and insulin resistance, particularly at moderate to high doses, and with intermediate to high risk compared to other atypical antipsychotics, possibly via the same unknown pharmacologic mechanism postulated to be active for some other atypical antipsychotics.

1.3.5 Aripiprazole

This agent is a D2 dopamine receptor partial agonist (DPA, D2 partial agonist), a major differentiating pharmacologic feature compared to serotonin dopamine antagonists that are silent antagonists at D2 receptors. Because of its D2 partial agonist actions, aripiprazole is theoretically an atypical antipsychotic with reduced EPS and hyperprolactinemia despite not having 5HT2A antagonist properties at higher affinity than its affinity for D2 receptors (i.e., 5HT2A lies to the right of D2, unlike almost every other atypical antipsychotic) (Figure 9). In addition, aripiprazole has 5HT1A partial agonist actions that are more potent than its 5HT2A antagonist actions, but less potent than its D2 binding affinity and this property hypothetically contributes to its atypical antipsychotic clinical properties, as discussed earlier in this section.

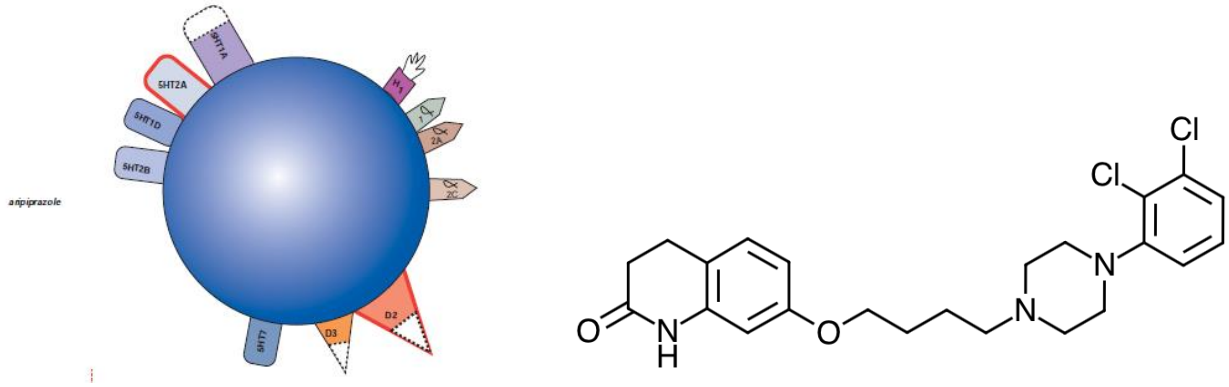

Figure 9: Aripiprazole's pharmacological profile (Stahl 2013) and chemical structure.

Aripiprazole is effective in treating schizophrenia and mania, and is also approved for use in various child and adolescent groups, including schizophrenia (age 13 and older), acute mania/mixed mania (age 10 and older), and autism-related irritability in children ages 6–17 in USA. Aripiprazole lacks the pharmacologic properties normally associated with sedation, namely, M1-muscarinic cholinergic and H1-histaminic antagonist properties, and thus is not generally sedating. A major differentiating feature of aripiprazole is that it has, like ziprasidone and lurasidone, little or no propensity for weight gain, although weight gain without dyslipidemia can be a problem for some, including children and adolescents. Furthermore, there seems to be little association of aripiprazole with dyslipidemia, elevation of fasting triglycerides, or insulin resistance (Stahl 2013). In fact, as with ziprasidone and lurasidone, when patients with weight gain and dyslipidemia caused by other antipsychotics switch to aripiprazole, there can be weight loss and lowering of fasting triglyceride levels. The pharmacologic properties that make aripiprazole different in terms of its lower metabolic risk are uncertain, but could be explained if aripiprazole lacks the ability to bind to postulated receptors that mediate insulin resistance and hypertriglyceridemia.
Aripiprazole is approved as an antidepressant for augmenting SSRIs/SNRIs in treatment-resistant major depressive disorder, and although not specifically approved, is often used as well in bipolar depression. How aripiprazole works in depression as compared to how it works in schizophrenia is of course unknown, but its potent 5HT1A partial agonist and 5HT7 antagonist properties are theoretical explanations for potential antidepressant actions, as these would be active at the low doses generally used to treat depression. It is also possible that partial agonist actions at both D2 and D3 receptors mean that aripiprazole could act more as an agonist than as an antagonist at dopamine receptors at low doses, in fact slightly boosting rather than blocking hypothetically deficient dopamine neurotransmission in depression, but this is unproven.
So, is aripiprazole the perfect "Goldilocks" D2 partial agonist? Some believe it is "too hot," meaning that it is too much of an agonist and not enough of an antagonist (Figure 4) , and that aripiprazole would thus be optimized if it were more of an antagonist, noting that aripiprazole can sometimes have dopamine agonist-like actions, such as being activating in some patients, causing mild agitation instead of tranquilization and antipsychotic actions, and can also cause nausea and occasionally vomiting. Also, high doses of aripiprazole sometimes do not seem to deliver sufficient antipsychotic efficacy in some very difficult-to-treat patients; in some psychotic cases, higher doses beyond a certain point are no more effective or even slightly less effective than somewhat lower doses (Stahl 2013).

On the other hand, some believe that aripiprazole is "too cold", meaning that it is too much of an antagonist because it can have antagonist-like actions such as causing akathisia in some patients, which is often decreased by dose reduction or by administering an anticholinergic agent or a benzodiazepine. In this case, aripiprazole might be improved by closer placement towards the agonist part of the spectrum shown in Figure 4. The truth is that there is no Goldilocks drug that fits every patient. In late-stage clinical development are drugs that are both more antagonist on the spectrum than aripiprazole. Soon there may be a portfolio of partial agonist options to customize the needs of individual patients, since one size cannot fit all.

1.3.6 Ziprasidone

Ziprasidone is another atypical antipsychotic with a novel pharmacological profile. The major differentiating feature of ziprasidone is that it has little or no propensity for weight gain, despite its moderate 5HT2C and H1 antagonist actions (Figure 10).

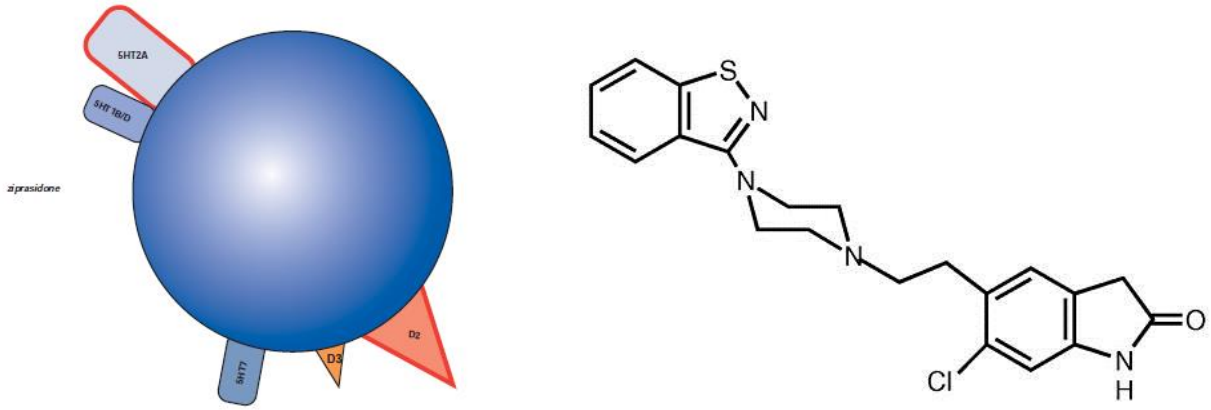

Figure 10: Ziprasidone's pharmacological profile (Stahl 2013) and chemical structure.

Furthermore, there seems to be little association of ziprasidone with dyslipidemia, elevation of fasting triglycerides, or insulin resistance. In fact, when patients who have developed weight gain and dyslipidemia from high-risk antipsychotics are switched from those antipsychotics to ziprasidone, there can be weight loss, and often lowering of fasting triglycerides, while continuing to receive treatment with ziprasidone.
The pharmacologic properties that make ziprasidone different in terms of its lower cardiometabolic risk are unknown, but could be explained if ziprasidone lacks the ability to bind to receptors postulated to mediate insulin resistance and hypertriglyceridemia. Ziprasidone is unusual as well because of the way it is dosed, namely twice a day and with food. Failure to give with about a 500 calorie meal can result in lowering oral absorption by half and inconsistent efficacy. Earlier concerns about dangerous QTc prolongation by ziprasidone now appear to be unjustified. Unlike iloperidone, zotepine, sertindole, and amisulpride, ziprasidone does not cause dose-dependent QTc prolongation, and few drugs have the potential to increase ziprasidone's plasma levels (Stahl 2013).

Any antipsychotic that prolongs QTc interval – and this includes several conventional and atypical antipsychotics – should be given cautiously to patients receiving other drugs known to prolong QTc interval, but routine EKGs are generally not recommended. It is obviously prudent to be cautious

when using any atypical antipsychotic or psychotropic drug in patients with cardiac problems, or in patients taking other drugs that affect cardiac function, or in those with a history of syncope or a family history of sudden death, and this is part of the routine risk–benefit calculation that is made for each individual patient prior to prescribing any of the atypical antipsychotic drugs. Ziprasidone has an intramuscular dosage formulation for rapid use in urgent circumstances. Ziprasidone has several pharmacologic properties suggesting it might have antidepressant actions, including 5HT2C, 5HT7, 5HT1B/D, and α2 antagonism and 5HT1A partial agonism, and weak norepinephrine and serotonin reuptake blockade but has never been proven to have antidepressant actions in large clinical trials (Stahl 2013).

Chapter 2.
Use of Atypical Antipsychotics in Child and Adolescent Psychiatry

The use of AAPs has expanded in clinical practice, and these agents are now prescribed for the treatment of aggressive behavior, behavioral dyscontrol, disruptive behavior disorders, and as an adjunctive treatment for aggression associated with other disorders, including attention-deficit/hyperactivity disorder (ADHD) (Olfson et al., 2012; Teixeira et al., 2013; Findling et al., 2005; Birnbaum et al., 2013; Lohr & Honaker 2013; Edelsohn et al., 2016). There are clinical guidelines for the treatment of specific disorders (i.e. schizophrenia, autism spectrum disorder [ASD], and tic disorders) that incorporate the use of antipsychotics (AACP 2015; Park et al., 2016; Lamberti et al., 2016), as well as a Practice Parameter from the American Academy of Child and Adolescent Psychiatry (AACAP) on the use of atypical antipsychotics. This Practice Parameter cites an the evidence base for using specific atypical antipsychotics to treat schizophrenia/psychosis, bipolar disorder, disruptive behavior disorders, Tourette syndrome, tic disorders, and autism/irritability in children. Prescribing antipsychotics in youth raises concerns about the risk of cardiometabolic problems, weight gain, movement disorders, sedation, and the possible impact of the medications on the developing brain. Furthermore, the AACAP recommendations note that the acute and long-term safety of these agents have not been fully evaluated (AACP 2016).

Though Food and Drug Administration (FDA) indications for the use of antipsychotics in the pediatric population are limited to the treatment of adolescent schizophrenia, bipolar mania, irritability associated with autism, and Tourette syndrome, there is an evidence base for off-label use (Rettew et al., 2015). Off-label prescribing (OLP) consists of the use of a drug for indications and/or at doses that have not been approved by local health authorities. Thus, OLP is more frequent in pathologies and populations in which few medications have been evaluated and approved, e.g., children (Palmaro et al., 2015), pregnant women and elderly individuals (Carton et al., 2015). OLP is particularly frequent in psychiatry (Malhi & Boyce 2011). Thirty-six to 93.2% of AP prescriptions were off-label in children and adolescents (Pathak et al., 2010; Marsanic et al., 2012; Baeza et al., 2014; Procyshyn et al., 2014; Rodday et al., 2014).

Zuddas et al. in 2011 reviewed randomized controlled studies on the use of atypical antipsychotics in treating non-psychotic disorders in youth, using efficacy and safety indices as measures of effectiveness (Zuddas et al., 2011). They found that the efficacy of these drugs was higher when treating mania, extreme mood variability, irritability, aggression, and disruptive behavior than when treating psychotic symptoms in schizophrenia. While all the atypical antipsychotics reviewed seemed to work well for schizophrenia, the drugs have different safety profiles. The authors provided clinical guidance on the choice of antipsychotic for the individual pediatric patient based on the safety profile of each medication along with specific risk factors (Zuddas et al., 2011).

In 2003, Treatment Recommendations for the use of Antipsychotics for Aggressive Youth (TRAAY) provided recommendations on the use of antipsychotics in youth with a variety of psychiatric disorders accompanied by externalizing behaviors (Pappadopulos et al., 2003). T-MAY (treatment of maladaptive aggression in youth), published in 2010, provides recommendations on assessment, diagnosis, and treatment of aggression disorders, including the possible use of antipsychotics if severe aggression continues after undertaking psychosocial treatment and/or

medication for underlying disorders (CERTs 2010). The Treatment of Severe Childhood Aggression (TOSCA) study, of children with ADHD, co-occurring oppositional or conduct disorder, and serious physical aggression, found that adding risperidone to parent training and stimulant medication was more effective than treatment without risperidone, though the effect sizes ranged from small to moderate (Gadow et al., 2014). The authors acknowledged that analyses of longer-term augmented treatment at 3 and 12 months might have different outcomes, including the risk for adverse effects. The authors also underscore that the results apply to severe irritability and aggression in children diagnosed with ADHD and caution against generalization beyond that population (Gadow et al., 2014). Park et al. found that almost 1 in 10 antipsychotic-treated youth were diagnosed with ASD and/or ID, and 1 in 6 youth with ASD received antipsychotics (Park et al., 2016).

A continuous increase in the off-label use of antipsychotics was identified during the last years. From 1996 to 2011, a 3.8-fold increase in the off-label use of both FGAs and SGAs was identified, in addition to an 18.1-fold increase in only SGAs prescribed for subjects aged 18 or less in North America (Ronsley et al., 2013). In patients aged 12 to 22 years, the percentage of patients who received at least one antipsychotic was 53.6% in 1997, 74.1% in 2002, and 69.4% (Gilat et al., 2011). The prescription increase was the highest in male adolescents (Hsu et al., 2013; Alessi-Severini et al., 2012; Edelsohn et al., 2016).
Risperidone was the most often prescribed drug (Baeza et al., 2014; Liu et al., 2014; Scheifes et al., 2013; Bachmann et al., 2013); however, a recent increase in aripiprazole OLP was also identified (Pathak et al., 2010). Haloperidol was the most prescribed off-label FGA. In preschoolers, a study conducted between 1991 and 1995 indicated that the use of off-label antipsychotics was substantially less frequent compared with psychostimulants and antidepressants (Zito et al., 2000). In another study conducted in 2001, antipsychotics represented 17% of the psychotropic medications, with 96% SGAs (Zito et al., 2007).
The most frequent off-label indications for antipsychotic use in children and adolescents were attention deficit hyperactivity disorder (ADHD), conduct disorders, oppositional disorders, pervasive developmental disorders, depression, tics, schizophrenia, bipolar disorders, and anxiety disorders (Baeza et al., 2014; Owens et al., 2010; Koelch et al., 2009; Penfold et al., 2010; Edelsohn et al., 2016). In the US, concurrent SGA use was important in patients included in Medicaid programs (Kreider et al., 2014). Similarly, in Europe, patients with lower social and economic status received significantly more AP prescriptions (Koelch et al., 2009). However, other data have not confirmed these previous findings.

In youth who received low-income assistance, general practitioners and other non-psychiatrists were more frequent prescribers of off-label antipsychotic use for anxiety disorders (79%), ADHD (75%), depression (52%), and pervasive developmental disorder (52%) (Alessi-Severini et al., 2012). The Treatment of Early Onset Schizophrenia Spectrum Disorders study (TEOSS), a larger, publicly funded, four-site, randomized, double-blind, controlled clinical trial, compared olanzapine (2.5–20 mg/day), risperidone (0.5–6.0 mg/day), and molindone (10–140 mg/day) for the treatment of patients age 8–19 years (mean 13.8; less than one-third with age 16 or older) with a diagnosis of schizophrenia (66%) or schizoaffective disorder (34%) over a period of 8 weeks (Sikich et al., 2008). A total of 119 patients were randomized. At the end of the 8 weeks, the response rate

(defined as at least a 20% reduction in the Positive and Negative Symptom Scale score plus the completion the 8- week acute treatment phase) was not different in the olanzapine (34%), risperidone (46%), and molindone (50%) groups.
Within the limitations imposed by the study sample size, TEOSS found no evidence to support the superiority of these SGA over a conventional antipsychotic. Although not different in efficacy, the three TEOSS medications showed a distinctive different safety profile: olanzapine induced more weight gain, hypercholesterolemia, and insulin elevation; risperidone increased serum prolactin; and molindone caused akathisia. The more recent introduction of ziprasidone and aripiprazole, with their specific tolerability profile, has further increased the heterogeneity of the SGA category with respect to safety/tolerability. Consequently, the safety/tolerability profile of these mediations and its implications for physical health, subjective well-being, and treatment adherence have emerged as the main considerations in the choice of an antipsychotic in youth (Arango et al., 2004).
The data in children and adolescents are overall consistent with those in adults, where a wide heterogeneity in tolerability profile within both first- and second-generation antipsychotics has been documented, with no evidence of specific efficacy of SGA on negative symptoms (Leucht et al., 2008). Moreover, also the SGA can, with a varying degrees, cause extrapyramidal adverse effects (Correll, 2008b), and metabolic adverse effects can emerge during treatment also with first-generation antipsychotics (Correll and Carlson, 2006; Correll, 2008a), thus blurring the separation between these two categories of antipsychotics. There are indications that children are more sensitive than adults to the metabolic adverse effects of SGA, as well as to the extrapyramidal effects of the first-generation antipsychotics (Correll et al., 2006). Children tend to gain proportionately more weight and do so more rapidly during treatment than adults (Correll and Carlson, 2006). In a recent randomized trial comparing olanzapine versus quetiapine, in adolescent patients with a first psychotic episode, the increment in weight was 15.5 kg and 5.5 kg over 6 months respectively. These increments are rarely seen in adults (Arango et al., 2009). Consistently across studies and like in adults, olanzapine seems to be especially prone to inducing metabolic adverse effects and related adverse health outcomes (Sikich et al., 2008; Fraguas et al., 2008; Castro-Fornieles et al., 2008). Based on currently available data, it appears that olanzapine cannot be considered a first-line antipsychotic medication for the treatment of children and adolescents. Because drug-induced metabolic changes can persist over time and may not be fully reversible upon drug discontinuation, the implications for distal health outcomes can be profound. Age-inappropriate weight gain and obesity increase the risk for a variety of negative outcomes, such as diabetes, hyperlipidemia, and hypertension, which are major risk factors for cardiovascular diseases and reduced quality of life and life expectancy (Correll and Carlson, 2006).
Also the effects on prolactin may be more marked in adolescents than in adults. One analysis combining the data from five clinical trials in 5–15 year old children treated with risperidone found a rapid rise of serum prolactin after starting treatment with a peak by 2 months, followed by a gradual return to normal levels by 5 months (Findling et al., 2003). However, in a different study, in 5–17 year old children with autism, the risperidone-induced increase in prolactin, though declining, was still significantly evident after 22 months of treatment (Anderson et al., 2007). In another study, hyperprolactinemia was present in 78.6% of youths treated with SGA for less than a month, and in 48.5% of those treated for longer than 1 year (Laita et al., 2007).
Prolactin increase is an issue especially for children and adolescents treated with risperidone (Staller, 2006; Sikich et al., 2008), but can occur with other antipsychotics as well, including

olanzapine (Dittmann et al., 2008), while aripiprazole seems to decrease prolactin plasma levels (Findling et al., 2008). Since youths may be less likely to express concern about sexual dysfunction, prolactin elevations may persist at subclinical levels. The long-term consequences of such elevations are currently unknown (Correll and Carlson, 2006).

In addition to the intrinsic pharmacological activity of the prescribed medications, treatment safety depends on the quality and intensity of the clinical management of the patients. The development of clinical guidelines for minimizing metabolic and endocrine adverse effects of antipsychotics children and adolescents represents a useful advancement (American Diabetes Association et al., 2004; Correll and Carlson, 2006; Correll, 2008a,b). Physical examination and both personal and family history taking before starting antipsychotic treatment can identify patients at high risk for metabolic syndrome, and periodic measurements of weight, body mass index, waist circumference, blood pressure, serum lipid and glucose during treatment can lead to early recognition of drug-induced adverse effects.

Measuring serum prolactin is currently not routinely recommended by many experts, but reserved to cases with clinical symptoms of hyperprolactinemia (Correll, 2008b). However, reports that some children treated with antipsychotics present with very high increases in prolactin during the first few months of treatment that in some cases is sustained, and the role of hyperprolactinemia in osteoporosis and reproductive problems are reasons for concern (Vitiello et al., 2009).

While the safety profile during acute and intermediate treatment has been evaluated, the distal benefit/risk ratio during long-term treatment remains to be determined.

Research is also needed to understand the mechanisms underlying antipsychotic-induced toxicities in order to develop effective preventive and treatment strategies.

Chapter 3.
Cardiometabolic Adverse Effects

Although all atypical antipsychotics share a class warning for causing weight gain and risks for obesity, dyslipidemia, diabetes, accelerated cardiovascular disease, and even premature death, there is actually a spectrum of risk among the various agents.

High metabolic risk – clozapine, olanzapine

Moderate metabolic risk – risperidone, paliperidone, quetiapine, iloperidone (weight only)

Low metabolic risk – ziprasidone, aripiprazole, lurasidone, iloperidone (low for dyslipidemia), asenapine, brexpiprazole?, cariprazine?

The pharmacologic mechanisms for what propels a patient taking an atypical antipsychotic along the "metabolic highway" (Figure 11) of these risks are only beginning to be understood. The "metabolic highway" begins with increased appetite and weight gain, and progresses to obesity, insulin resistance, and dyslipidemia with increases in fasting triglyceride levels (Figure 11) (Stahl 2013).

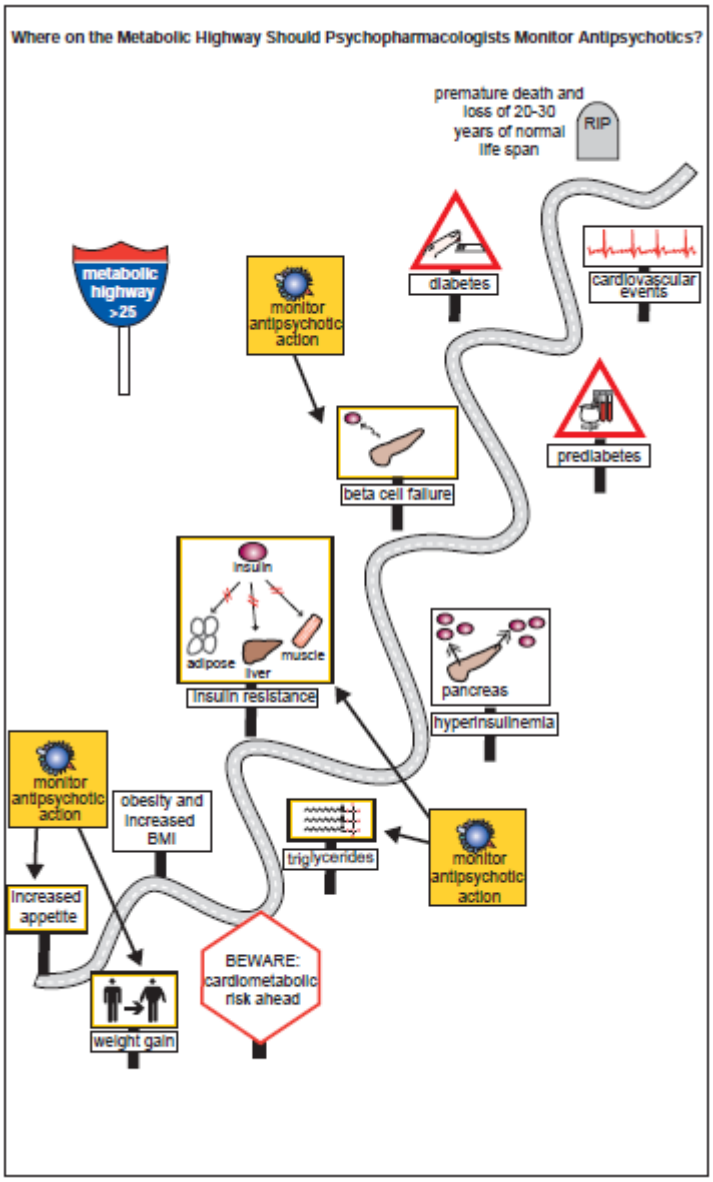

Figure 11: The Metabolic Highway (Stahl 2013). Monitoring on the metabolic highway. Where on the metabolic highway should psychopharmacologists monitor antipsychotics? Key stages along the metabolic highway where antipsychotics can produce cardiometabolic risks are the places where the actions of these drugs should be monitored. Thus, there are at least three "on" ramps where the cardiometabolic risk of some atypical antipsychotics can enter the metabolic highway, and they are all shown here. First, increased appetite and weight gain can lead to elevated body mass index (BMI) and ultimately obesity. Thus, weight and BMI should be monitored here. Second, atypical antipsychotics can cause insulin resistance by an unknown mechanism; this can be detected by measuring fasting plasma triglyceride levels. Finally, atypical antipsychotics can cause sudden onset of diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar syndrome (HHS) by unknown mechanisms, possibly including blockade of M3-cholinergic receptors. This can be detected by informing patients of the symptoms of DKA/HHS and by measuring fasting glucose levels.

Ultimately, hyperinsulinemia advances to pancreatic β-cell failure, prediabetes and then diabetes. Once diabetes is established, risk for cardiovascular events is further increased, as is the risk of premature death (Figure 11). So if the treatment start in early lifetime, probably we add more chance to develop to this "highway". Receptors associated with increased weight are the H1 histamine receptor and the 5HT2C serotonin receptor, and when these receptors are blocked, particularly at the same time, patients can experience weight gain. Since weight gain can lead to obesity, and obesity to diabetes, and diabetes to cardiac disease along the metabolic highway (Figure 11), it seemed feasible at first that weight gain might explain all the other cardiometabolic complications associated with treatment with those atypical antipsychotics that cause weight gain. This may be true, but only in part, and perhaps mostly for those agents that have both potent

antihistamine properties and potent 5HT2C antagonist properties, notably clozapine, olanzapine, quetiapine, as well as the antidepressant mirtazapine (Stahl 2013).
However, it now appears that the cardiometabolic risk of certain atypical antipsychotics cannot simply be explained by increased appetite and weight gain, even though they certainly do represent the first steps down the slippery slope towards cardiometabolic complications.
That is, some atypical antipsychotics can elevate fasting triglyceride levels and cause increased insulin resistance in a manner that cannot be explained by weight gain alone. When dyslipidemia and insulin resistance occur, this moves a patient along the metabolic highway towards diabetes and cardiovascular disease (Figure 11). Although this happens in many patients with weight gain alone, it also occurs in some patients who take atypical antipsychotics and prior to their gaining significant weight, as if there is an acute receptor-mediated action of these drugs on insulin regulation.
Another rare but life-threatening cardiometabolic problem is known to be associated with atypical antipsychotics: namely, an association with the sudden occurrence of diabetic ketoacidosis (DKA) or the related condition hyperglycemic hyperosmolar syndrome (HHS). The mechanism of this complication is under intense investigation, and is probably complex and multifactorial.
In some cases, it may be that patients with undiagnosed insulin resistance, prediabetes or diabetes, who are in a state of compensated hyperinsulinemia on the metabolic highway (Figure 11), when given an atypical antipsychotic agent, become decompensated because of some pharmacologic mechanism associated with these drugs. Because of the risk of DKA/HHS, it is important to know the patient's location along the metabolic highway prior to prescribing an antipsychotic, particularly if the patient has hyperinsulinemia, prediabetes, or diabetes. It is also essential to monitor and manage these risk factors (Stahl 2013).
Specifically, there are at least three stops along the metabolic highway where a psychopharmacologist should monitor a patient taking an atypical antipsychotic and manage the cardiometabolic risks of atypical antipsychotics (Figure 11). This starts with monitoring weight and body mass index to detect weight gain, and fasting glucose to detect the development of diabetes. It also means getting a baseline of fasting triglyceride levels and determining whether there is a family history of diabetes. The second action to monitor is whether atypical antipsychotics are causing dyslipidemia and increased insulin resistance, by measuring fasting triglyceride levels before and after starting an atypical antipsychotic (Figure 11). If body mass index or fasting triglycerides increase significantly, a switch to a different antipsychotic that does not cause these problems should be considered. In patients who are obese, with dyslipidemia, and either in a prediabetic or diabetic state, it is especially important to monitor blood pressure, fasting glucose, and waist circumference before and after initiating an atypical antipsychotic. Best practices are to monitor these parameters in anyone taking any atypical antipsychotic. In high risk patients, it is especially important to be vigilant for DKA/HHS, and possibly to reduce that risk by maintaining the patient on an antipsychotic with lower cardiometabolic risk. In high-risk patients, especially those with pending or actual pancreatic β- cell failure as manifested by hyperinsulinemia, prediabetes, or diabetes, fasting glucose and other chemical and clinical parameters can be monitored to detect early signs of rare but potentially fatal DKA/HHS (Stahl 2013).
It's quite known that psychiatric patients have a reduced life expectancy of 15–25 years relative to the general population, with cardiovascular disease being the leading cause of death (Correll &Nielsen 2010). In addition, risk of sudden cardiac death (SCD) is more than doubled in patients on antipsychotics (Ray et al., 2009, Osborn et al., 2015). Suboptimal antipsychotic treatment may

increase risk of attempted suicide, with overdose as a common method, and even when treated effectively with first- or second-generation antipsychotics (FGAs, SGAs), psychiatric patients are still less likely to receive proper somatic treatment, follow screening programs, and attend regular health checks (Marder et al.m, 2004; Nielsen et al. 2011). As we said above, SGAs contribute to the increased mortality gap due to the association with life-shortening metabolic adverse effects, including weight gain, dyslipidemia, and type 2 diabetes mellitus (T2DM) but also a variety of cardiovascular adverse effects ranging from minor and frequent complications, including sinus tachycardia (ST) and orthostatic hypotension (OH), to more serious arrhythmias such as the polymorphic ventricular tachycardia Torsades de Pointes (TdP), may cause SCD. In adults we have to consider other mechanisms behind the susceptibility to these cardiovascular risk factors including smoking, alcohol abuse, poor diet, sedentary lifestyle, and stress, should also be considered as a piece in this puzzle (Henderson et al., 2015). Currently, most clinical concern focuses on prolonged cardiac repolarization. Some antipsychotics (e.g., clozapine) have been associated with other lifethreatening cardiovascular complications, including myocarditis and cardiomyopathy, for which the pharmacological mechanisms are more unclear. Finally, antipsychotics may also cause SCD from myocardial infarction (MI), most likely by increasing well-known cardiovascular risk factors (Nielsen 2011).

These potentially fatal complications raise the question of whether electrocardiogram (ECG) monitoring is indicated in all patients on antipsychotics, in patients with cardiovascular risk factors, or only in patients with symptoms of cardiovascular disease. However, current recommendations on routine ECG monitoring are divergent (Shah 2014, Polcwiartek et al., 2016). So we plan a little clinical overview about the most important cardiovascular implications.

3.1 Electrocardiographic adverse effects

a) Torsades de Pointes and sudden cardiac death

The World Health Organization has defined SCD as an unexpected death occurring within 1 h of symptom onset if witnessed, and if unwitnessed, within 24 h after the person has last been observed alive and symptom free (Nielsen et al., 2011). Some antipsychotics have been associated with a markedly increased SCD risk. One potential mechanism is via blockade of the delayed rectifier potassium current (*I*Kr), a subunit of the potassium channel protein Kv11.1, which is encoded by the *human ethera-go-go-related gene* (*hERG*). This blockade is known to be dose dependent and can prolong cardiac repolarization, seen as corrected QT (QTc) prolongation on the ECG. In clinical practice, QTc prolongation often causes concern, as it may progress to TdP in rare cases. If not managed immediately, TdP can deteriorate into ventricular fibrillation and cause SCD (Nielsen et al., 2011).

SCD occurs twice as often in patients on antipsychotics, with an incidence of approximately 15/10,000 years of drug exposure (Nielsen et al., 2011). However, the exact association with TdP remains largely unknown, partly because the TdP diagnosis is unconfirmed in most cases. In addition to the high prevalence of cardiovascular risk factors in psychiatric patients, capturing antipsychotic-induced TdP is further challenged by the rarity of the complication and need for ECG monitoring at the time of the event. Another major challenge is that routine autopsy procedures to provide precise explanation for the cause of death are not always utilized.

Recently, international pharmacovigilance studies have detected signals of torsadogenicity for commonly used antipsychotics over a 7-year period using the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database (Poluzzi et al., 2013; Raschi et al., 2013). Most TdP cases were associated with olanzapine (*n* = 189), quetiapine (*n* = 186), clozapine (*n* = 178), ziprasidone (*n* = 167), risperidone (*n* = 151), haloperidol (*n* = 125), and aripiprazole (*n* = 46). Similar findings have been observed in France, Germany, and Italy using national spontaneous reporting systems (Raschi et al., 2016).
Out-of-hospital cardiac arrest (OHCA) is one clinical manifestation of SCD and captured in the nationwide Danish Cardiac Arrest Register. By using this register, Weeke et al. found that the FGAs haloperidol and levomepromazine and the SGA quetiapine were all associated with OHCA, but further studies are warranted to clarify the underlying mechanisms of these associations (Weeke et al., 2014). Furthermore, in a recent meta-analysis of observational studies, Salvo et al. compared odds ratios (ORs) of SCD between antipsychotic users and non-users (Salvo et al., 2015). SCD risk was increased with thioridazine (OR = 4.58), clozapine (OR = 3.67), risperidone (OR = 3.04), haloperidol (OR = 2.97), olanzapine (OR = 2.04), and quetiapine (OR = 1.72). To some extent, this corroborates data from the FAERS database, where most SCD cases were associated with quetiapine (n = 934), clozapine (n = 900), olanzapine (n = 712), risperidone (n = 486), haloperidol (n = 239), aripiprazole (n = 230), and ziprasidone (n = 161) (raschi et al., 2013). Because of the challenges in estimating the exact risk of antipsychotic-induced TdP and eventually SCD, one of the most widely used surrogate markers for TdP remains the QTc interval. The upper normal threshold for clinical concern is defined as 460 ms for children, 450 ms for men, and 470 ms for women (Goldenberg et al., 2006). Although a QTc interval ≥ 500 ms warrants discontinuation of antipsychotic treatment, QTc prolongation alone does not always predict TdP on an individual level (Nielsen et al., 2011).

b) Corrected QT prolongation

Important and high-quality QTc data from antipsychotics are available from the Pfizer 054 study conducted by Pfizer Inc. and requested by FDA as part of the registration process for ziprasidone (Zeldox study, 2000). In this randomized controlled trial (RCT), QTc prolongation (Bazett's formula) between haloperidol, olanzapine, quetiapine, risperidone, thioridazine, and ziprasidone was compared in 164 patients with schizophrenia. All antipsychotics except for thioridazine were administered at the highest therapeutic dose, and the QTc interval was measured both in the absence and presence of a metabolic inhibitor. A cross-sectional study conducted in Italy confimerd a link between antipsychotic polypharmacy and QTc prolongation and supported the current guidelines that recommend avoiding the concurrent use of two or more antipsychotic drugs (Nosè et al., 2016). In phase I of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a large federally funded study, QTc prolongation between olanzapine, perphenazine, quetiapine, risperidone, and ziprasidone was compared in 1,493 patients with schizophrenia (Lieberman et al., 2005). In a recent meta-analysis of RCTs, Leucht et al. compared QTc prolongation of amisulpride, aripirazole, asenapine, haloperidol, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, and ziprasidone with placebo in 43,049 patients with schizophrenia (Leucht et al., 2013). While QTc prolongation with ziprasidone is found to be greater compared with other

SGAs, it does not necessarily imply that ziprasidone is more torsadogenic and associated with increased SCD risk (Citrome 2011). Only rare TdP cases have been reported in patients on ziprasidone as well as other SGAs (Hasnain & Vieweg 2014). In these cases, causality was not clearly determined owing to several risk factors for QTc prolongation. Although clinically relevant QTc prolongation may be found with ziprasidone, a QTc interval ≥ 480 ms or baseline increase ≥ 60 ms is rare. Olanzapine, quetiapine, and risperidone appear to have a modest QTc prolongation when used in therapeutic doses (Hasnain & Vieweg 2014). In contrast, sertindole was never approved for the US market, although approved in Europe in 1996. In the premarketing phase, 12 sudden deaths and 23 cases of syncope were reported. It was later withdrawn, in 1998, due to increased risk of arrhythmias and sudden death but relaunched on the European market in 2005 (Karamatskos et al., 2012; Pae 2013).
Interestingly, aripiprazole has a rather QTc-shortening effect, with small decreases of 0.7 and 4 ms compared with placebo and active controls, respectively (Polcwiartek et al., 2015). In addition, the overall safety and tolerability of aripiprazole remains more favorable compared with other SGAs across approved indications (Pae 2009, Nielsen et al., 2010). Lurasidone is generally thought to be cardiovascular safe, although it has been associated with a QTc prolongation of 7.5 ms (120 mg/day) and 4.6 ms (600 mg/day), with no apparent dose-dependent relationship. Clinically, such minor QTc changes with aripiprazole and lurasidone are not relevant, especially because a QTc interval > 500 ms or baseline increase > 60 ms is rare (Shah 2014). Clozapine deserves special attention, as it has been associated with substantial heart rate increases, which may complicate QTc measurement. Current clinical studies assessing the QTc effect of clozapine use Bazett's formula and overestimate QTc prolongation. So whether clozapine actually cause QTc prolongation is an unresolved question (Nielsen 2012).

In 2014, we have conducted a preliminary study of a total of 60 patients (55 M/5F, mean age 10.2+2.6 years, range 4-15 years), receiving a new prescription of aripiprazole or risperidone in monotherapy and monitored before and after two months from the beginning of antipsychotic treatment (Germanò et al. 2014). No clinically relevant modifications of QT interval were found. Jensen et al. evaluated the effect of antipsychotics on QTc interval in youth in a huge systematic review followed to a meta-analysis (Jensen et al., 2015). A total of 55 studies were meta-analyzed, evaluating 108 treatment arms covering 9 antipsychotics and including 5,423 patients with QTc data (mean age = 12.8 $\pm$ 3.6 years, female = 32.1%). Within group, from baseline to endpoint, aripiprazole significantly decreased the QTc interval (-1.44 milliseconds, CI = - 2.63 to - 0.26, p = .017), whereas risperidone (p 1.68, CI = p 0.67 to p 2.70, p = .001) and especially ziprasidone (p 8.74, CI = p 5.19 to p 12.30, p < .001) significantly increased QTc. Compared to pooled placebo arms, aripiprazole decreased QTc (p = .007), whereas ziprasidone increased QTc (p < .001). Compared to placebo, none of the investigated antipsychotics caused a significant increase in the incidence of the 3 studied QTc prolongation measures. Based on these data, the risk of pathological QTc prolongation seems low during treatment with the 9 studied antipsychotics in otherwise healthy youth (Jensen et al., 2015). Alda et al. didn't observe mean increase in QTc or in heart rate in a 12 months follow-up study. SGA seemed to have a safe heart side effect profile in the child and adolescent population (Alda et al., 2016).

c) Thorough QT studies and corrected QT as a surrogate marker

Risk of pro-arrhythmic effects of antipsychotics should be estimated from all available preclinical, clinical, and pharmacovigilance data. Since 2005, the thorough QT (TQT) study, a standardized phase I study assessing a drug's ability to prolong cardiac repolarization, has been mandatory before approval of new drugs (ICH Guidelines 2016). Normally, healthy subjects receive therapeutic and eventually supra- therapeutic doses to detect small QTc changes, as this could indicate a more substantial effect in patients at high risk for torsade. A negative TQT study is defined as a study, where the upper limit of the one-sided 95% confidence interval for QTc prolongation excludes 10 ms. With this definition, a QTc prolongation of approximately 5 ms is the threshold of regulatory concern. In case of a positive TQT study, more safety studies are warranted before drug approval can be granted. However, in a recent cost-effectiveness analysis of TQT studies, Bouvy *et al.* found that in patients on antipsychotics, health benefits resulting from assessing antipsychotics for their QTc-prolonging effect did not outweigh costs associated with regulation such as requirement for ECG monitoring (Bouvy et al., 2012).

Although it is clear that most antipsychotics are associated with QTc prolongation, it is rather difficult to rank each antipsychotic for this risk, as various ECG measurements and study designs have been used. However, in a recent clinical overview, Fanoe et al. derived weighted recommendations for commonly used antipsychotics using pharmacovigilance data from several international databases, and whether they were assessed in a TQT study (Fanoe 2014). Aripiprazole, olanzapine, perphenazine, and zuclopenthixole were categorized as class *A* drugs (i.e., no risk of QTc prolongation or TdP) with the highest level of evidence. Amisulpride, chlorprothixene, clozapine, flupentixol, levomepromazine, paliperidone, quetiapine, risperidone, and sulpiride were categorized as class *B* drugs (i.e., propensity of QTc prolongation). Finally, haloperidol, pimozide, sertindole, and ziprasidone were categorized as class *B* drugs (i.e., pronounced QTc prolongation, documented TdP cases, or other serious arrhythmias). Of all antipsychotics, only iloperidone, paliperidone, and ziprasidone have been assessed in a TQT study (Fanoe et al., 2014; Hasnain & Vieweg 2014).

With imprecise measurement, need for heart rate correction, and poor predictability of TdP, it is debated whether the QTc interval is an optimal surrogate marker for TdP (Porthan et al. 2009; Nielsen et al., 2011). To reduce the effect of heart rate on QT measurements, the QT interval is most commonly corrected using Bazett's formula. Because of the tendency of Bazett's formula to overcorrect at heart rates > 70 beats/min, other correction methods, including Fridericia's or Framingham's formula, are also commonly used (Rabkin & Cheng 2015). Given the limitations of correction and substantial diurnal variation in the QTc interval, longitudinal QTc assessment should be interpreted cautiously when concomitant heart rate changes are present (Nielsen et al., 2011). Therefore, alternative surrogate markers, including QT dispersion, QT dynamics, T-wave asymmetry, T-wave flatness, T-wave morphology combination score, and Tpeak– Tend interval, have emerged (Kanters et al., 2008; Graff et al, 2009; Graff et. Al, 2010). In fact, prolongation of the TpTe interval, measured in lead V5, is considered independently associated with SCD, and it can be a suitable risk indicator even when the QTc is within range or not measurable due to prolonged QRS duration (Panikkath et al., 2011; Bieganowska et al., 2013).

To date, the studies investigating the cardiovascular risk of SGAs have exclusively considered the QTc and QTd variations. We introduced this measurement in monitoring cardiosafety of stimulant

and found more detailed data even if no pathological values was identified with this adding methods (Lamberti et al., 2015). These markers may be more sensitive at identifying patients at high risk for torsade, thereby providing more reliable data than the QTc interval, yet the complexity of these measurements has limited their clinical implementation.

d) Patients at high risk for torsade

Special attention should be paid to patients at high risk for torsade, as the clinical features associated with TdP development include genetic, clinical, and drug-related factors. Patients with type 2 long QT syndrome, an autosomal dominant condition with *hERG* mutations, have increased TdP risk that is magnified when exposed to QTc-prolonging drugs (Nielsen et al., 2011). Other genetic risk factors also include poor metabolizers of for example, cytochrome P450 (CYP) 2D6, where plasma levels of drugs and cardiotoxic metabolites are substantially increased after a given dose (Brown et al., 2004). In addition, bradycardia, conduction disturbances, coronary artery disease, structural myocardial disease, including post-myocardial infarction and cardiomyopathy, and electrolyte derangements, particularly hypokalemia, may also increase TdP risk. Female sex and age ≥ 65 years are also well-established risk factors. Among psychiatric patients, other risk factors, including polypharmacy, drug doses above recommended therapeutic ranges, exposure to drugs of abuse such as central nervous system stimulants, and attempted suicide with overdose, are not uncommon (Nielsen et al., 2011)[8]. However, antipsychotic polypharmacy is not directly associated with increased mortality, but using more than one antipsychotic is closely related to high-dose prescribing (Gallego et al., 2012; Takeuchi et al., 2015)[47, 48]. This could potentially increase TdP risk, as QTc prolongation for many antipsychotics is dose dependent.

3.2 Brugada syndrome

Antipsychotics have also been associated with blockade of the fast sodium current (*I*Na) encoded by the *sodium channel, voltage-gated, type V, α-subunit* (*SCN5A*). This blockade reduces peak sodium influx causing altered voltage gradients such as those seen in Brugada syndrome (BrS), a genetic ion channel disease that also causes SCD (Sicouri et al., 2008).

On the ECG, three types of Brugada repolarization patterns can be recognized in the right precordial leads V1–3. Type 1 Brugada ECG is diagnostic of BrS and characterized by coved STsegment elevations ≥ 2 mm (0.2 mV) followed by T-wave inversions. Type 2 Brugada ECG is characterized by ST-segment elevations ≥ 2 mm with saddleback appearance and either positive or biphasic T waves. Finally, type 3 Brugada ECG is characterized by ST-segment elevations < 1 mm with saddleback or coved appearance. Patients with a non-diagnostic baseline ECG suggestive of BrS (i.e., types 2–3) must undergo a sodium-channel blocker challenge (e.g., ajmaline or flecainide) to potentially unmask a diagnostic type 1 Brugada ECG (Sicouri et al., 2008).

Approximately, 15% of probands with BrS have *SCN5A* mutations, and > 100 mutations in *SCN5A* have been identified. However, considering the *I*Na-blocking effect of some antipsychotics, certain patients may be susceptible to BrS phenotype. Common risk factors include high fever, alcohol and cocaine toxicity anesthetics, antidepressants, antihistamines, α-adrenergic agonists, β- blockers, hypokalemia, hyperkalemia, and hypercalcemia (Sicouri et al., 2008).

Evidence of antipsychotic-induced BrS is rather limited, especially no clinical studies have assessed BrS risk with commonly used antipsychotics. Cases have only been reported with clothiapine,

haloperidol, loxapine, and phenothiazines (e.g., cyamemazine, thioridazine, and trifluoperazine) (Rouleau et al., 2001; Adler et al., 2013). However, most of these cases were considered as type 1 Brugada ECG and occurred after either drug combinations or overdose making causality less clear.

3.3 Sinus tachycardia

Most antipsychotics increase heart rate, on average by 10–15 beats/min (Leung et al., 2012). ST, defined as heart rate ≥ 100 beats/min, is most pronounced at treatment initiation and during up-titration indicating a dose-dependent relationship. The mechanism is a combination of both anticholinergic and antiadrenergic effects, as well as indirect effects via central autonomic regulation and baroreceptor reflexes. Antipsychotics blocking muscarinic M2 receptors reduce the parasympathetic tone and increase
heart rate. Antipsychotics may also block adrenergic α1 receptors causing vasodilation and reflex tachycardia (Leung et al., 2012). Finally, antipsychotic-induced akathisia may also contribute to ST (Chavez & Poveda 2006). ST risk is increased with antipsychotics with high affinity for muscarinic M2 receptors, including clozapine (25%), quetiapine (7%), risperidone (5%), and low-potency FGAs (e.g., chlorpromazine).
In contrast, risk is lower with other SGAs, including olanzapine (3%) and ziprasidone (2%) (Feinstein 2002; Michelsen & Meyer 2007).
This is also evident with aripiprazole due to almost lack of anticholinergic and antiadrenergic effects (Polcwiartek et al. 2016).
Rarely, ST warrants treatment, as tachyphylaxis occurs after weeks. In the initial phase, a slower up-titration may diminish ST. While ST is transient with most antipsychotics, this is not always the case with clozapine. Although ST is usually asymptomatic, it could be the first sign of lifethreatening conditions, including myocarditis, cardiomyopathy, or neuroleptic malignant syndrome.
Accompanying fever and flu-like symptoms during the first months of treatment warrant measurement of troponin plasma levels or echocardiography to exclude myocarditis. Newly occurring ST during long-term clozapine treatment should raise suspicion of cardiomyopathy (Nielsen et al., 2013).
After excluding other somatic causes of ST, dose reduction of clozapine may alleviate ST. It is unclear whether asymptomatic ST warrants treatment, as evidence of long-term consequences is limited. If treatment is indicated, a cardioselective β-blocker should be first choice. However, β-blockers should not be initiated within the first months, as tolerance to the heart rate-increasing effect of clozapine is likely to occur after 4–6 weeks of treatment. In addition, β-blockers may also complicate the diagnosis of myocarditis, where ST is a key symptom. In case of lack of response to or intolerability of β-blockers, ivabradine should be considered (Nielsen et al. 2013).

3.4 Heart rate variability

In addition to ST, the anticholinergic effect of antipsychotics have also been associated with reduced heart rate variability, a measure of beat-to-beat (RR) interval variations. Heart rate variability is not only a predictor of SCD but also of MI, as well as progression of coronary artery disease and heart failure. While patients on clozapine have decreased heart rate variability, other antipsychotics, including haloperidol, olanzapine, and risperidone, do not appear to decrease heart rate variability (Leung et al., 2012).

Other complications

Antipsychotics may also cause a wide range of more uncommon ECG abnormalities that potentially could contribute to increased SCD risk. Most SGAs, including clozapine, olanzapine, quetiapine, risperidone, and ziprasidone, have been associated with bradycardia, atrial and ventricular premature beats, atrial fibrillation, first-degree atrioventricular block, bundle branch block, QRS prolongation, ST-segment depression and elevation, and T-wave inversion (Chou et al., 2017). Especially, ST-segment and T-wave abnormalities are also present when clozapine is combined with fluvoxamine, a selective serotonin reuptake inhibitor that potently inhibits CYP1A2, thereby increasing clozapine plasma levels (Polcwiartek et al., 2016).

Regarding arrhythmia risk, *I*Kr and *I*Na are therefore not the only concerns. For example, bradycardia and heart block are caused by blockade of high-voltage (L-type) calcium channels that are responsible for conduction via the atrioventricular node and for sinoatrial node automaticity (Buckley & Sanders 2000).

3.5 Vascular adverse effects

e) Orthostatic hypotension

OH, defined as a decrease in systolic or diastolic blood pressure of ≥ 20 or ≥ 10 mmHg, respectively, within 3 min of standing, is a very common dose-dependent adverse effect of most antipsychotics (Leung et al., 2012). The mechanism by which antipsychotics cause OH is by blockade of adrenergic α1 receptors, and OH symptoms may be exacerbated by the sedating effect of some SGAs (e.g., clozapine) (Polcwiartek et al., 2016). Early identification of risk factors, including autonomic disorders, fluid imbalance, and polypharmacy affecting hemodynamics, as well as proper treatment can minimize the severity of OH. Based on data from phases I–III of the CATIE study, clozapine and quetiapine were found to have highest risk (24% and 27%, respectively), whereas aripiprazole, olanzapine, risperidone, and ziprasidone had lowest risk (≤ 6%). Among the more recently introduced SGAs, iloperidone exerts highest risk (19.5% compared with 8.3% in patients on placebo in a pooled analysis of RCTs), whereas risk is lower with asenapine and lurasidone (< 2%) (Gugger 2011). OH can delay or even prevent necessary dose titration to control symptoms and has been associated with syncope, transient cerebral ischemia, stroke, and MI. Some patients also do not effectively report symptoms of cerebral hypoperfusion and other complications to physicians due to their psychotic disorder (Gugger 2011). In addition, antihypertensive drugs should be used carefully when coadministered with antipsychotics.

g) Hypertension

While evidence of OH associated with antipsychotics is extensive, evidence for a hypertensive effect is more limited and contradictory (Henderson et al., 2004). Although hypertension, defined as blood pressure ≥ 140/90 mmHg, is not a contraindication to antipsychotic treatment, some antipsychotics may cause or even exacerbate hypertension. Common risk factors include underlying cardiovascular disease, smoking, and family history of hypertension or cardiovascular disease (Khasawneh & Shankar 2014).

Increased hypertension risk is associated with mid-potency FGAs (e.g., perphenazine) and the SGAs clozapine (4%), olanzapine (2%), and ziprasidone (1%), whereas risperidone and quetiapine are associated with a lower risk (< 1%) (Bodén et al., 2013).

3.6 Direct cardiac adverse effects

h) Myocardial infarction

It remains unclear whether antipsychotics increase MI risk (Brauer et al., 2011). Increased risk is associated with SGAs (e.g, amisulpride) and short-term treatment (i.e., ≤ 30 days), as well as the association is stronger in male patients, older patients, and patients with no cardiovascular risk factors (Brauer et al., 2013; Lin et al., 2014; Wu et al., 2015; Yu et al., 2016). In addition to amisulpride, both clozapine and risperidone have also been associated with increased risk (Feinstein 2002). Interestingly, a recent study found that 75% of MIs in patients with schizophrenia were unrecognized and propose that the absence of pain may be an important factor (Nielsen et al., 2015).

i) Myocarditis

Myocarditis, defined as an inflammation of the myocardium, associated with antipsychotics is a type I hypersensitivity reaction. Typically, it is of the eosinophilic type characterized by abundant eosinophils that release toxins, which induce apoptosis and necrosis of cardiomyocytes (Leung et al., 2012). Common risk factors include personal history of recent viral, bacterial, or parasitic infections, confirmed allergy to clozapine, and personal history of MI, pericarditis, cardiomyopathy, or heart failure (Polcwiartek et al., 2016). Clozapine is by far the most commonly used antipsychotic that has been associated with myocarditis, with an incidence as high as 3% (Ronaldson et al., 2015). Other antipsychotics include chlorpromazine, fluphenazine, haloperidol, olanzapine, quetiapine, and risperidone (Leung et al., 2012).
This life-threatening complication is commonly overlooked and may cause myocardial fibrosis, arrhythmias, and eventually SCD. It occurs within the first months of treatment and is diagnosed by ST along with ST-segment elevations on the ECG or increased troponin plasma levels. Patients may present with flu-like symptoms, fever, fatigue, and dyspnea. In case of myocarditis, antipsychotic treatment warrants discontinuation and, if indicated, patients should be treated with corticosteroids (Nielsen et al., 2013).

l) Cardiomyopathy

Cardiomyopathy, defined as a deterioration of the function of the myocardium, is considered a less common cardiovascular adverse effect of antipsychotics caused by untreated myocarditis as well as other factors. Usually, it is of the dilated type and onset occurs slower than myocarditis (Leung et al., 2012). Again, clozapine is most commonly associated with cardiomyopathy. Other antipsychotics include amisulpride and quetiapine. Although ECG signs are non-specific, they include ST along with P- and T-wave abnormalities and signs of left ventricular hypertrophy. In

addition, reduced pulse pressure (i.e., difference between systolic and diastolic blood pressure) can be found. Common symptoms include fatigue,
dyspnea, and tachypnea, symptoms that are difficult to separate from typical patients on clozapine. Diagnosis is confirmed with echocardiography. In case of cardiomyopathy, antipsychotic treatment warrants discontinuation and, if indicated, patients should receive appropriate heart failure treatment (Nielsen et al., 2013). However these last cardiological diseases are quite rare in children and adolescent.

In conclusion, prescription of antipsychotics should always be balanced between perceived clinical effect and burden of adverse effects. Initially, lowest therapeutic doses of antipsychotics should be prescribed, and polypharmacy should be avoided if possible. We recommend physicians to increase awareness of the cardiovascular safety of antipsychotics. However, all examinations should be symptom driven and routine monitoring should only be implemented in case of substantial evidence. Research will move to increase evidence of connection between the use of SGAs and cardiometabolic consequences.

Chapter 4.
Evaluation of ECG parameters in children and adolescents treated with second-generation antipsychotics: a 2-year prospective study

4.1 Background

As we said above, APs are increasingly prescribed in the pediatric population for the treatment of a number of psychiatric disorders such as psychoses, autism, attention deficit and hyperactivity disorder (ADHD), and aggressive behavior. These drugs are often preferred to traditional APs in reason of a better tolerability and safety profile. The use of second-generation APs in pediatric age has increased significantly in the last few years. However, a paucity of controlled studies provide a quantitative estimate of the relative risks associated with these agents in young populations in a long-term follow up. Both first- and second-generation AP are known to be associated with QT prolongation on the electrocardiogram (ECG), which predisposes patients to an increased risk of developing threatening ventricular arrhythmias such as torsade de pointes, and related sudden death (Drici and Priori, 2007; Haddad and Anderson, 2002; McNally et al., 2007; Ray et al., 2009; Vieweg, 2003). AP determine QT prolongation due to a dose-dependent effect on the myocardial repolarization by inhibiting the rapid component of the delayed potassium rectified current, which promotes potassium efflux from the ventricular myocytes (Haddad and Anderson, 2002; Nielsen et al., 2011; Roden, 2006). The mechanism is similar to the QT prolongation produced by many antiarrhythmic agents such as amiodarone and sotalol (Roden, 2006). QT interval prolongation is the most widely used surrogate marker for assessing the risk of torsade de pointes but it is considered somewhat imprecise, partly because QT interval changes are subject to measurement error. In particular, drug induced T-wave changes (e.g. flattening of the T-wave) may complicate the measurement of the QT interval. Furthermore, the QT interval depends on the heart rate and a corrected QT (QTc) interval is often used to compensate for this. Several correction formulas have been suggested, with Bazett's formula the most widely used. However, Bazett's formula overcorrects at a heart rate above 80 beats per minute and, therefore, Fridericia's formula is considered more appropriate to use in these cases (Lou et al., 2004). Several other surrogate markers for TdP have been developed but none of them is clinically implemented yet and QT interval prolongation is still considered the most valid surrogate marker (Nielsen et al., 2011). The QT interval monitoring, when corrected for heart rate, is widely used as predictor of lethal arrhythmias, as these are often preceded by a long QTc. Prolongation of the QTc interval beyond 500 ms and an increase in QTc greater than 60 ms from baseline have both been shown to predict torsades de pointes (Schwartz et al., 1993). Although QTc interval prolongation is widely used as marker of arrhythmic risk, it is considered only a rough indicator. Conversely QTc dispersion (QTd), a measure of the inter-lead variation in the QT interval (defined as the difference between maximum and minimum QT interval duration), was shown to be a more reliable predictor for cardiovascular mortality in the general population (Bogun et al., 1996; Cuddy et al., 2009; Rautaharju et al., 2009). In particular, a QTd of 120 ms has been demonstrated to be a strong correlate of inducible ventricular tachycardia and its predictive value was not influenced by gender, mean QTc, and left ventricular systolic function (Bogun et al., 1996). Despite the fact that metabolic and neurological adverse effects have been described well in children and adolescents for many SGAs (Caccia, 2013; Findling et al., 2008b; Ho et al., 2011; Maayan and Correll, 2011;

Margari et al., 2013; Migliardi et al., 2009; Pringsheim et al., 2011a), less detailed evaluations of the risk for effects on QTc interval on the electrocardiogram have been reported in pediatric population. Moreover, recent studies indicate that prolongation of the interval between the peak and the end of the T wave (T-peak to T-end, TpTe) on the 12-lead EKG can represent a new marker of ventricular arrhythmogenesis. In fact, prolongation of the TpTe interval, measured in lead V5, is considered independently associated with SCD, and it can be a suitable marker even when the QTc is within range or not measurable due to prolonged QRS duration (Panikkath et al., 2011; Bieganowska et al., 2013). To date, the studies investigating the cardiovascular risk of APs have exclusively considered the QTc and QTd variations. TpTe and TpTe/QT intervals, along with QTc and QTd modifications have not been investigated in the context of drug-related cardiovascular adverse effects of SGA. We performed a 2-year prospective follow-up evaluation of EKG parameters in a population of children and adolescents treated with second-generation APs. Finally, the differences between the different AP were also analyzed.

4.2 Subjects & Methods

Children and adolescent patients (mean age =10,29 ± 3,22 years, range 6–18 years), were enrolled into this prospective, naturalistic, not randomized, longitudinal study study to assess the arrhythmic risk of five SGA: Aripiprazole, Risperidone, Olanzapine, Clozapine and Quetiapine by analyzing the principal cardiovascular risk markers, namely QTc interval and TpTe intervals, and the main treatment-influenced factors, as well as the heart rate. Subjects consecutively attending our programs in the Unit of Child Neurology and Psychiatry of the University Policlinic of Messina between September 2013 and December 2016, and starting a treatment of SGA according to child psychiatrist's clinical judgment, were considered for the study. None of the included patients had a history, signs, or symptoms of cardiovascular, pulmonary or endocrine disorders.
Inclusion criteria were age <18 years at baseline, any psychiatric diagnoses from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5) (American Psychiatric Association 2013), first prescription of any SGA within 30 days prior to enrollment, and at least two visits during follow-up. At baseline, patients were classified as treatment naıve (no previous AP) or quasi-naıve (AP initiated in the 30 days prior to enrollment). A total of 155 subjects were asked to participate and accepted. Patients with an eating disorder diagnosis were excluded from the analysis (n = 11) to avoid interference with cardiac effects of malnutrition. Patients who did not have any recorded QTc measurement were also excluded (n = 20). Ultimately, a total of 124 patients were analyzed (Table 1). Concomitant treatment with antidepressants, anticholinergics, mood stabilizers, and benzodiazepines was permitted. The study was approved by the local ethics committee. Subjects and parents received detailed information about characteristics, potential adverse effects, and different treatment options for SGA.
All parents or legal guardians of participants gave written informed consent prior to enrollment, and subjects >12 years of age agreed to participate.

4.3 Clinical Assessment

Demographic and clinical characteristics of the sample were collected at baseline from parents or legal guardians and the patient. The diagnoses were made by child and adolescent psychiatrists,

based on the DSM-5 diagnostic criteria. Treatment information was evaluated at baseline and during follow-up (1, 3, 6, 12, 18 and 24 months) through exhaustive recording of the AP given and the dose administered. The concomitant medication received was also recorded.
A standard 12-lead ECG was performed with the patient in the supine position at baseline and at any of the follow-up visits. The ECG used at the site was Cardioline delta 3 plus.
The duration of QT intervals was measured manually, by an experienced cardiologist, in all leads in which the onset of the QRS complex and the return of T wave to baseline were clearly identified.
The QT duration was corrected for heart rate according to the Bazett's formula to produce QTc and averaged for all assessed leads (mean QTc). If respiratory sinus arrhythmia was present the QT interval was measured in all leads where RR intervals were almost equal. Heart rate, RR, PR and QRS intervals were also measured. QTd was calculated as the difference between the longest and shortest individual lead QTc. QTc intervals N450 ms or 60 ms longer than at baseline, and QTd N100 ms were considered abnormal (Correll et al., 2011). TpTe interval was measured from the peak of the T wave to the end of T wave in lead V5 (Pannikath et al., 2011). The TpTe/QT ratio was calculated as the ratio of TpTe in that lead to the corresponding QT interval (Antzelevitch et al., 2007; Shimizu et al., 2002). HR, RR, PR, and QRS intervals were also measured. QTd was calculated as the difference between the longest and shortest individual lead QTc. QTc intervals > 450 milliseconds or 60 milliseconds longer than at baseline and QTd > 100 milliseconds were considered abnormal (Correll et al., 2011; Germanò et al., 2014). Normal values for TpTe interval and for TpTe/QT ratio, calculated on V5 leads, were ranged from 4 milliseconds to 100 milliseconds (mean 63.3 ± 11.38 milliseconds, median 60 milliseconds) and from 0.12 to 0.29 (mean 0.195±0.0344, median 0.188), respectively (Bieganowska et al., 2013). All measurements were taken blind by two independent cardiologists who measured the QTc simultaneously, and the value used was the mean. The interobserver variability was <2%.

4.4 Data analysis

The baseline and post-treatment ECG data for the various measurements were collected using Microsoft Office Excel 2007 SP2 (Microsoft, Redmond, WA). The data were presented as mean ± SD. To identify differences in the five groups, ANOVA and the X^2 test were used. For the statistical analysis, only visits at which an ECG was performed (baseline, 12 and 24 month follow-up) were included.
Data analyses were performed using SPSS® for Windows® package. First the normality distribution of data was evaluated using the Kolmogorov– Smirnov statistics (K–S test) with Lilliefors' significance correction.
Then, the baseline/post-treatment measures were compared by mean paired-sample t test for the normally distributed data, and the Wilcoxon paired rank test for the non-normally distributed data.
Two sided tests were used and statistical significance was accepted at a $p < .05$ level. According to the intention-to-treat principle, data imputation of patients who withdrew were managed by assignment of an average value of outcome variable among those in that treatment group with complete data.

4.5 Results

The clinical and demographic characteristics of the 124 subjects included in the study are shown in Table 1. All patients received an SGA. Patients evaluated at each visit for each drug were: Aripiprazole n = 53, Risperidone n = 44, Quetiapine n = 10, Clozapine n = 9 and Olanzapine n = 8 (Tab. 1). As shown in Table 1, no differences were found into the five treatment. Demographic characteristics are shown in Table 1.

- Electrocardiographic changes

The mean, standard deviation and p values of the ECG measurements in total samples at baseline, 12 months and 24 months of SGA's treatment are shown in Table 2. No abnormal findings were observed in the ECG results at both times, including any changes in voltages, axes, or morphology. Moreover, there was no significant difference noted in QTc and QTd intervals between all determinations. No patient exhibited a QTc interval greater than 500 milliseconds or a QTd greater than 100 milliseconds, at both determinations. No change in TpTe values was found (Table 2), but a statistically significant increase in TpTe/ QTc ratio was found with respect to basal values (0,16±0.08 milliseconds vs 0,19±0.03 milliseconds; $p< 0,05$). There were no differences in all values at any time when comparing the two main AP drugs of our sample (aripiprazole and risperidone) (Table 3). However, only in patients treated with risperidone, a significant variation in QTd (QTd: 65,7±31,3 vs 57,8±15,5; $p< 0.05$) was observed between baseline and 2-year follow up values (Table 3).

4.6 Discussion

In this large sample with antipsychotic-naıve or quasi-naıve children and adolescents treated mainly with SGA, QTc and QTd intervals and heart rate did not increase during the 2 year follow-up.
In this sample, in keeping with other studies in pediatric populations (de Castro et al. 2008; Correll et al. 2011; Margari et al. 2013; Germanò et al., 2014), we did not find variations in QTc in relation to AP use either at baseline or during the longitudinal 24 month period. Although there are also some studies suggesting that SGA may increase QTc in pediatric populations, this prolongation seems to be significant only for ziprasidone (Jensen et al. 2015). There are studies that demonstrate a relationship between this increase and greater presence of schizophrenic spectrum disorders in pediatric samples (Correll et al. 2011). Moreover, recent studies have demonstrated ECG changes in adults with schizophrenia in comparison with healthy controls, even without the presence of AP treatment (Blom et al. 2014). In this study, there were no differences found when the sample was divided in two subgroups based on presence or absence of psychosis, in keeping with other studies in pediatric populations (de Castro et al. 2008).
It is important to emphasize that, even having selected less restrictive values for QTc changes (>440 ms) (Van Dorn et al. 2011), only a small proportion of patients (2.3%) presented values >440 ms at baseline, and it remained stable as the study progressed.
Further, it is important to highlight that the QTc values did not increase related to any of the five evaluated SGA, there were no cases in which QTc intervals were >500 ms, and no patients were discontinued on the basis of prolonged QTc. In our sample, QTc values decreased in patients treated with aripiprazole.

Studies demonstrate different effects on QTc prolongation by different AP, in both adult (Buckley and Sanders 2000) and pediatric populations (Labellarte et al. 2003). With regard to atypical drugs, it is worth mentioning ziprasidone, with some studies in adult (Keck et al. 2001) and pediatric (Blair et al. 2005; Jensen et al. 2015) populations reporting QTc prolongation; however, in the pediatric population, these results are questionable (Loebel et al. 2006). Another study (Correll et al. 2011) suggested a potentially low arrhythmogenic effect in adolescents with a normal baseline ECG receiving this medication. In our sample, most of the subjects were naïve to SGA (73,4%). The two main prescribed AP were analyzed individually (aripiprazole and risperidone) and no differences were found among them in terms of influence on QTc or other variables. This study was unable to evaluate the effect of clozapine, quetiapine and olanzapine because of the limited number of patients involved. When ECG parameters need to be monitored for information regarding the repolarization, TpTe values could be very helpful. TpTe is the result of the global distribution of the repolarization process. In a recent study, it was significantly and independently associated with increased odds of SCD in subjects with coronary artery disease. Thus, TpTe measurement may extend the value of repolarization beyond the QTc, particularly in situations where QTc is either normal or not valid due to prolongation of QRS duration. Prolonged TpTe has potential for enhancement of SCD risk stratification and warrants evaluation in additional, larger populations (Panikkath et al., 2011). This new ECG marker can be very useful when patients have instead cardiological pathologies (such as hypertension, Brugada syndrome, or others) (Karaagac et al., 2014) or metabolic diseases (like diabetes) before starting psychiatric pharmacological treatment. In fact, normal values of TpTe/QT ratio are relatively narrow, so it can be easier to find patients with high risks of torsades de pointes. Also in our sample this ratio reached statistical significance even if values were always inside the normality. Finally, it must be emphasized that this study had a 24 month longitudinal design with patients with SGA. The fact that this is a naturalistic study in both inpatient and outpatient children and adolescents allows its results to be generalized to different treatment settings.

4.6.1 Limitations

First, the naturalistic, nonrandomized design of the study and the risk of selection and attrition bias were limitations of our study. It should also be pointed out that there was important loss of patients to follow-up during the study, which led us to use mixed models in the statistical analysis in order to limit its impact. The limited use of certain AP with a higher risk of cardiovascular side effects, such as ziprasidone, clozapine, and FGA, do not allow us to draw conclusions regarding these AP. The study permitted the use of concomitant medications. The limited number of patients on other drugs precluded us from assessing the potential effects of those drugs on the cardiological intervals. We have also to correlate cardiological variables to metabolic pathways (such as BMI).

4.7 Conclusions

The SGA evaluated in this study (aripiprazole, risperidone, clozapine, olanzapine, and quetiapine) appear to be safe in the child and adolescent population, with regard to QTc, QTd, TpTe and heart rate. This is backed up in this study by the fact that there were no major arrhythmias reported.

This study demonstrates that AP appear to be safe from the point of view of electrocardiographic side effects in the pediatric population, in keeping with recent papers (Jensen et al., 2015; Alda et al., 2016), as our sample does not present QTc or QTd prolongation or increased heart rate. Further evidence-based studies are needed on cardiac safety in children treated with AP in order to improve the quality of care of children with mental health disorders, and the awareness among patients and practitioners of the side effects associated with these drugs. However, AP treatment have to be included in a more comprehensive rehabilitation route. Research have to show new findings in pharmacogenomics and neurobiology of each diseases that would conduct to personalized treatments in order to increase effectiveness of drug treatments and reduce costs and short/long side effects of our patients.

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