

Quetiapine: An Objective Evaluation of Pharmacology, Clinical Uses and Intoxication

Ramadhan Oruch^{1*}, Ian F Pryme², Ole Bernt Fasmer³ and Anders Lund⁴

¹Department of Biochemistry and Molecular Biology, School of Medicine, Najran University, Najran, Kingdom of Saudi Arabia

²Department of Biomedicine, School of Medicine, University of Bergen, Bergen, Norway

³Department of Clinical Medicine, Section of Psychiatry, University of Bergen, Bergen, Norway

⁴Division of Psychiatry, Haukeland University Hospital, Norway

*Corresponding Author: Ramadhan Oruch, Department of Biochemistry and Molecular Biology, School of Medicine, Najran University, Najran, Kingdom of Saudi Arabia.

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Abstract

Quetiapine is an antipsychotic drug that belongs to the group of nonconventional agents. Mainly used to treat schizophrenia, bipolar depressive disorder, and exacerbations of manic and depressive episodes of this condition. It is also used to prevent these episodes of exacerbation, beside its many off-label uses. Atypical antipsychotics treat negative symptoms of psychosis without causing extra sedation, and help schizophrenics to integrate into society and, in addition, to remove unwanted extrapyramidal symptoms that conventional agents are known to exert. Unfortunately, these agents, including quetiapine, have other drawbacks the most serious of which are those associated with the disease spectrum of metabolic syndrome and, furthermore, the many interactions quetiapine may be involved in with other drugs in cases of polypharmacy. This review gives an update on quetiapine and provides a guideline to psychiatric caregivers, and importantly, undergraduates of medicine and pharmacy students on clinical uses (both dedicated and off-label), pharmacology, pharmacopeia, and intoxication that might occur following its use, and how to treat such a condition.

Keywords: Quetiapine; Psychotropic; Drug Interactions; Free Radicals; Metabolic Syndrome; Suicide; Insomnia; EPS

Abbreviations

QTP: Quetiapine; EPS: Extra Pyramidal Symptoms; PD: Parkinson's Disease; ROS: Reactive Oxygen Species; BD: Bipolar Depressive Disorder; HPD: Haloperidol; CLZ: Clozapine; OLZ: Olanzapine; SERT (5-HTT): Serotonin Transporter; NET: Norepinephrine Transporter; DAT: Dopamine Transporter; NMDA: Glutamate receptor; VGCC: Voltage Gated Calcium Channel; hERG: Human Ether-a-go-go-Related Gene.

Introduction to Psychiatric Diseases

Psychosis (schizophrenia), major depression, bipolar depression and anxiety neurosis, are corner morbidities that psychiatrists encounter in their clinics and psychiatric institutions. The obscurity around the pathophysiology behind the etiology of these ailments and thus lack of proper selective therapeutic agents makes the radical treatment of these conditions challenging. Treatment of these diseases costs the national economies millions of dollars. The prevalence of mental disorders varies in different societies, dependent on many factors, for example: age, sex (gender), culture, education, economic (being in the labor force or not) and social status (not married or being in an unstable relationship).

Statistic findings from different countries and regions confirm that common mental disorders are highly prevalent globally, affecting people across the whole world. In a major survey study concerning the prevalence of mental diseases using the secondary data across the Medline, PsycINFO, EMBASE and PubMed databases, 174 surveys across 63 countries were identified. From those surveys 155 provided period prevalence and 85 surveys estimated lifetime prevalence. Meta-analysis based on logit-transformed prevalence cross all studies showed approximately 1 in 5 respondents were identified to fulfill the criteria for a common mental disorder during the 12 months preceding assessment at some time during their lifetimes.

Concerning gender as a parameter of this meta-analysis showed that women had higher rates of mood and anxiety disorders, while men exhibited higher rates of substance-use problems, with a similar pattern for lifetime prevalence. The same study showed also evidence of regional variation in the prevalence of common mental disorder, the underlying reasons of which remain to be investigated [1]. This major statistical study reflects the importance of antipsychotic agents worldwide for the well-being and prosperity of mankind.

Side effects of Psychopharmaca

We will briefly discuss the important and well-known side effects of antipsychotics in general, that is both 1. Typical (conventional, or what is known as 1st generation) antipsychotics and 2. Atypical (nonconventional or 2nd generation) antipsychotics. For detailed nomenclature and classification see [2].

Long term effects: Since a course of treatment with antipsychotics lasts for months, it is rational to discuss issues concerning the long-term effects of antipsychotics.

- In general, use of antipsychotic decreases life expectancy - attributed to metabolic disorders and weight gain and its consequences [3]. This is especially the case for antipsychotic agents that belong to the category of 2nd generation ones. Patients in the geriatric age group who are on antipsychotic drugs, have a reduced life span in comparison to those in the normal population of the same age group, as demonstrated in many meta-analytic studies [4]. We should not forget the sequelae of events associated with grey matter loss from the brain i.e. dementia and Alzheimer's disease-like symptoms, occurring in those who use antipsychotic agents for long periods [5]. It is expected that these structural changes in the cerebral cortex decrease life expectancy of such individuals [6].
- According to a case report, QTP has been blamed to worsen the clinical situation of depersonalization (derealization) disorder [7]. Sometimes, and as a consequence of misdiagnosis of this psychiatric disorder as a schizophrenia, doctors may prescribe antipsychotics to such individuals. In such cases antipsychotics devastate and worsen the clinical situation of such individuals [8].
- Polypharmacy of antipsychotic agents should be avoided as much as possible, because it is not an evidence-based practice and might be harmful because it will increase the total dose of these neuroleptics and thus widen the spectrum of both side effects and interaction of these drugs with one another [9]. Sometimes a combination of antipsychotic agents can be considered acceptable, especially in cases of treatment resistance schizophrenia [10]. Sometimes establishment of a precise diagnosis can be a challenge even for experts. In such cases, one might need to combine two antipsychotics concomitantly in order to achieve the optimal or desired therapeutic effect on the patient who may have responded poorly to certain forms of antipsychotic therapy. The reason behind this practice is that we do not yet know exactly how these agents precisely work, at least at the cellular level.
- Drug induced akathisia: An extrapyramidal system (EPS) side effect, that is an involuntarily movement disorder associated with a feeling of restlessness and lacking the ability to stay still. This is most prominent in the legs. In some individuals, this restlessness and uneasiness may end in suicide [11]. 1st generation antipsychotics are mostly blamed for this totally unwanted effect,

although other psychotropics can also induce such tardive side effects [12]. With respect to psychotropic drugs, the underlying physiology behind this phenomenon is believed to be the inhibition of the dopamine system of the CNS [11].

- Tardive dyskinesia: As the name indicates, it's onset may occur a time after commencing antipsychotic treatment. The symptoms may remain even after stopping the treatment (as a withdrawal complication) [13]. The situation is more prominent with 1st generation antipsychotics and the antiemetic metoclopramide [14]. This disorder includes repetitive involuntary movement of different parts of the body, especially the face (grimacing, smacking of lips and sticking-out the tongue). In these individuals one may also observe jerking or writhing movements, thus resulting in decreased function.
- Withdrawal syndrome (discontinuation syndrome): When the therapeutic dose of an antipsychotic is gradually decreased or abruptly stopped. The symptoms typically include: Agitation, restlessness, depression, insomnia, cognitive dysfunction and worsening of the negative symptoms for which the antipsychotic is mainly indicated [15]. The psychiatrist should be careful when deciding to switch (change) one antipsychotic to another, since a rapid change in a drug can induce these withdrawal symptoms. If indicated, this should be done smoothly and gradually [16]. One should evaluate cross-titration when switching from say a 1st generation to a 2nd generation agent.

Short-lived (transient) side effects: For simplicity, we are going to subdivide these into two subcategories: I. Rare side effects and II. Common ones.

Although rare adverse effects happen seldom, occurring in less than 1% of antipsychotic drug users. The following is worthy of mention:

- Blood dyscrasia: This includes agranulocytosis, leucopenia, neutropenia (decrease in the number of neutrophils), with the consequences of decreased cell mediated immunity in these individuals and their liability to get opportunistic infections. This is not uncommon in patients on clozapine therapy.
- Neuroleptic malignant syndrome (NMS): Includes manifestations and laboratory findings of which the most important are: hyperthermia, muscle rigidity, autonomic instability, change in mental status (subsequent coma) and elevated serum creatine kinase levels [17].
- Metabolic syndrome: Both 1st and 2nd generation antipsychotics can cause the syndrome, probably though by different mechanisms. It is scientifically documented that 2nd generation drugs (especially clozapine, olanzapine, zotepine and quetiapine) cause type II diabetes (Non-Insulin Dependent Diabetes; NIDD) [18]. In this regard females manifest this complication more frequently than males and, interestingly, with 1st generation drugs too [19]. In an American study it is asserted that Afro Americans are more liable than Caucasians to develop this subtype of diabetes [20]. Other complications of metabolic syndrome also include the following: thromboembolism, ischemic heart diseases (myocardial infarction) and stroke. In addition, it is important to mention here that weight gain, caused by use of an antipsychotic, can also contribute to metabolic syndrome by precipitating the complications associated with the syndrome. It is believed that antipsychotic-induced obesity is resultant of the fact that these drugs antagonize histamine H₁ and serotonin 5-HT_{2c} receptors [21], and probably also interact with other neurotransmitter systems of the CNS [22].
- Seizure: In those who use one of the following: pimozide, amisulpride, thioridazine, sertindole or ziprasidone [23].

Common adverse effects: the incidence being 1% - 50% among antipsychotic users.

- CNS: Sedation (especially chlorpromazine, asenapine, clozapine, olanzapine, quetiapine, zotepine), anxiety, headache.

- Peripheral nervous system: Orthostatic hypotension.
- Extrapyramidal side effects (EPS): Tremors, Parkinsonism, akathisia, dystonia.
- Endocrine and hormonal: Hyperprolactinemia (antagonism of dopamine), galactorrhea, gynecomastia, impotence and sexual dysfunction, osteoporosis.
- Anticholinergic side effects: Blurred vision, constipation (or sometimes diarrhea, although not as an anticholinergic side effect), dry mouth (or hypersalivation), hypoventilation. Again, this is further evidence supporting the assertion that we do not know exactly how these drugs act on a neuronal basis.

Quetiapine (QTP), physical properties, and a short history

Quetiapine was developed by AstraZeneca in 1985 as a 2nd generation antipsychotic medication, primarily to treat schizophrenia and bipolar depression. As a pure agent, it exists as a white powder, the molecular formula is: C₂₁H₂₅N₃O₂S. Chemically, it is a dibenzo thiazepine derivative, it has a molecular weight of 383.51 g/mole. Pure quetiapine is moderately soluble in water (3.29 mg/mL), this favors the agent to make hydrogen bonds in water and 0.9% NaCl (polar solvents). The agent has no isomers. It has the IUPAC Name: 2-[2-(4-benzo[b][1,4] benzothiazepin-6-yl)piperazin-1-yl] ethoxy] ethanol.

It was approved as a 2nd generation antipsychotic agent by the US-FDA in 1997. For therapeutic purposes the agent exists as a fumarate salt (C₄H₄O₄), see figure 1.

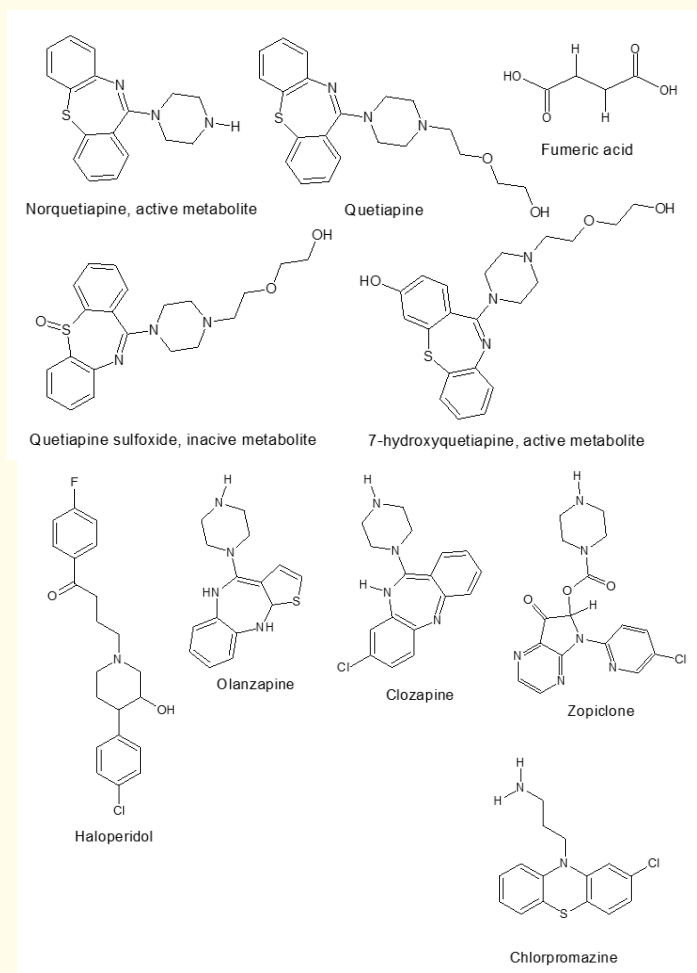


Figure 1: Chemical structures of the discussed drugs.

Synthesis of quetiapine: This commences from its ketone form (dibenzothiazepinone), where the lactam ring (cyclic amide) is dehydrated with phosphoryl chloride (POCl_3), then using a nucleophilic substitution reaction a side chain is added to the lactam amide to produce quetiapine, see figure 2.

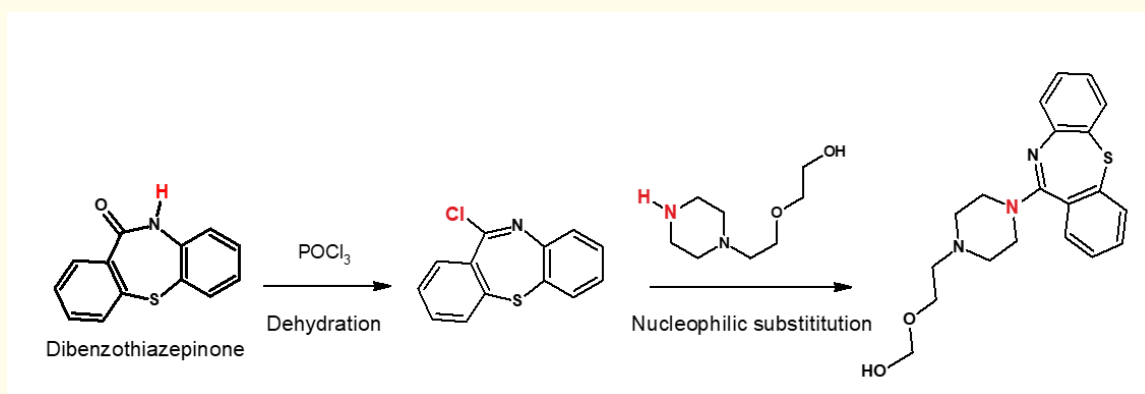


Figure 2: Synthesis of quetiapine.

Metabolism of quetiapine

Since QTP is a water-soluble agent, it is only available for oral use, existing as tablets, slow release tablets and suspension forms.

The fumarate form of the drug is rapidly absorbed from the gastrointestinal system (GIT) and reaches peak concentration values within 90 minutes. In tablet forms the bioavailability of the drug is almost 100% after the 1st pass from GIT to serum. The absorption of QTP is negligibly affected by food. The major active metabolites of this agent are norquetiapine (N-desalkylquetiapine) and 7-hydroxy-quetiapine, see figure 1.

Being water soluble, QTP binds to plasma proteins to the extent of 83% in which state it exerts its therapeutic effects. It reaches peak blood levels in about 2 hours and has a plasma half-life of 6 hours [24].

The drug is metabolized by the liver and only 1% of it is excreted in the unchanged state. The major metabolic pathways are sulfoxidation (sulfoxide metabolite) and oxidation to (acid metabolite). These metabolites are inactive pharmacologically. Catabolism of the drug is achieved by the microsomes of liver cells where the cytochrome P450 3A4 isoenzyme (isozyme) is involved in the process (smooth endoplasmic reticulum of hepatocytes). This is the reason behind the wide range of drug interactions QTP exerts with other agents metabolized by the same microsomal system and thus it modifies (induces/inhibits) the pharmacological actions of co-administered drugs and also its own therapeutic actions and gives rise to unwanted effects (pharmacodynamics). The inactive metabolites (quetiapine sulfoxide) and (O-desalkylquetiapine) are excreted in the stool and urine. Measurement of these metabolites can be useful in evaluating drug adherence, in adjustment of the optimal dose, and in the assessment of cases of acute poisoning.

Clinical uses of quetiapine

Dedicated uses

The approved indications for the use of QTP in psychiatry in the western world are the following:

- Treatment of schizophrenia,
- Treatment of bipolar depressive disorder,
- Treatment of severe to moderate exacerbation (episodes) of manic episodes of bipolar disorder,
- Treatment of depressive exacerbation (episode) of bipolar disorder,
- Prevention of relapses of manic or depressive exacerbations in bipolar patients who responded to previous QTP therapy.

Any therapeutic use of QTP apart from in the conditions mentioned above is off-label.

It was approved as a mood stabilizer (bipolar disorder) in 2004 and in 2009 as an antidepressant (adjunct) with other antidepressants. Its common use as an anxiolytic (sedative) is an off-label use.

Off-label uses of Quetiapine

Generalized anxiety disorder (GAD) and insomnia

GAD includes the following: insomnia, asthenia, unexplained headache and paresthesia in extremities, hypertonia, myalgia, dysphagia, gastric upset, diarrhea, disattention, irritability, sweating and dyspnea (DSM-5, 2013). This morbidity is a common cause of incapacity at the workplace in the United States. Quetiapine could be prescribed here off-label with the aim to alleviate the above-mentioned symptoms [25]. Insomnia is one of the accompanying signs that patients complain about when consulting their doctor, and small doses of QTP have been used to treat this ailment [26]. The major psychiatric complaints of these individuals are anxiety and/or depression. Small doses of QTP have been found to be beneficial although not always recommended, because of the wide spectrum of side effects the drug can cause. One should also bear in mind the possibility of the wide spectrum drug interactions that QTP can exhibit when used concomitantly with other psychotropics, or drugs of other categories, because of the coexistence of other morbidities, for example, as might be the case within the geriatric age group of patients [27]. Benzodiazepines (short course of use, up to 14 days), antihistamines, zopiclone and others could be tried since these are probably safer. Still, these also can cause drug “hangover” and tolerance (benzodiazepines) but there is probably a lower likelihood of interaction with other drugs.

Major depressive disorder (MDD) “monotherapy”: Quetiapine has been used as a monotherapy in MDD, but the drawback here is sedation which is undesirable for a depressive patient. This 2nd generation antipsychotic has also been used as an add-on or adjunct to other antidepressants such as tricyclic antidepressants (TCA) and/or selective serotonin reuptake inhibitor (SSRI) preparations [28]. The drawback here is as an expected interaction of QTP with these psychotropic agents. This practice is not recommended unless it is absolutely indicated.

Alzheimer’s disease and dementia: Earlier QTP was prescribed to decrease agitation, but this was found not to be useful. Indeed, it worsened the intellectual capacity of these individuals [29]. The same was also found to be true for agitation occurring in senile dementia (chronic organic brain syndrome).

Delirium: This is an organic psychiatric syndrome, characterized by fluctuations in consciousness, perception, cognition and behavior. A study from 2000 involved two groups of patients (10 - 11/group) where the first used QTP fumarate and the second group (control group), used haloperidol. Each of these two groups included in the study showed an improvement of > 50% with QTP fumarate or haloperidol as a first choice of treatment for their complaints. Quetiapine, the 2nd generation antipsychotic, was better tolerated in the first group than the 1st generation antipsychotic haloperidol (the standard agent to treat delirium) which was used in the second group.

Indeed, these two alternatives (QTP and HPD) have equal effects in the treatment of delirium, QTP though, can cause more sedation and sleepiness which is a drawback regarding this agent [30].

Being a 2nd generation antipsychotic it is identical in effect to other 2nd generation drugs such as risperidone and olanzapine [31]. It is believed that these two latter 2nd generation antipsychotic agents, also including QTP, may supersede the typical antipsychotics. Some authors believe that the pharmacology of QTP may allow it to be used in the treatment of delirium and provide sedation without causing significant extrapyramidal side effects [32]. Haloperidol, however, remains the drug of choice in treatment of delirium.

This might be attributed to the fact that HPD is much more potent than QTP [33]. We should not generalize the therapeutic effects of 2nd generation antipsychotics either, because these are neither identical in their efficacy nor in their spectrum of side effects.

Obsessive compulsive disorders (OCD): Selective serotonin reuptake inhibitors (SSRIs) have been used to treat this morbidity, in addition to other complimentary psychotherapeutic measures. A tricyclic antidepressant (TCA) e.g. clomipramine, is also another choice, but it is not superior to SSRIs because of the wide spectrum side effects TCA exhibit.

According to the guidelines of the National Institute of Clinical and Health Excellence (NICE), a British institution, psychiatrists have since 2006 started to recommend the prescription of 2nd generation antipsychotic agents to treat OCD cases that did not respond to SSRIs [34]. Since then agents such as risperidone and/or olanzapine have been in use to treat OCD. A review study in 2014, depending on secondary data, found aripiprazole to be effective in the short term. Authors of the same study found “no evidence for the effectiveness of QTP or olanzapine in comparison to placebo” about therapeutic outcome.

Indeed, the efficacy of quetiapine is limited by the insufficient number of studies [35]. Another study states that QTP may be useful when used as an add-on to an SSRI in treatment-resistant OCD. The same study stated also that the drugs belonging to the 2nd generation antipsychotics are often poorly tolerated and have metabolic side effects that limit their use. Since none of the atypical antipsychotics are useful when used alone [36], polypharmacy will be inevitable, in other words a “swamp” of drug interactions may occur. Quetiapine may be only useful when employed in addition to an SSRI in treatment-resistant OCD. A final thing to be mentioned in this context is that conventional antipsychotic agents (1st generation agents) have no place in the spectrum of drug therapy of OCD.

Personality disorders

Borderline personality disorder (BPD)

The cornerstone in the management of these individuals is psychotherapy.

In the guide lines of 2009, the British National Institute for Health and Clinical Excellence (NICE), remarked the following: firstly, because of weak evidence and secondly, due to serious side effects of these medications, “Drug treatment should not be used specifically for BPD or for the individual symptoms or behaviors associated with the disorder”.

On the other hand, there are studies suggest that quetiapine may be a choice regarding treatment of affective symptoms and impulsivity in BPD [37]. According to Perella, *et al.* with a daily average dose of 450 mg of QTP, affective symptoms and signs in the form of dysregulation and aggression, seen clinically with BPD, can be ameliorated [38]. In this study 6 patients out of 29 were dropped from the study in an early phase, because of serious side effects including transient thrombocytopenia in 2 of them. In a randomized double blind, placebo-controlled study, low (150 mg daily) and moderate (300 mg daily) doses of QTP-XR (extended-release) were compared in BPD.

Participants treated with 150 mg/day of QTP showed a significant reduction in the severity of BPD symptoms compared to those who received placebo. Emerging side effects of treatment: dry mouth, change of appetite and excessive sedation, were additional important reasons for eliminating the above-mentioned participants from the study [39]. This finding illustrates the fact that antipsychotics, including QTP, are hazardous drugs and should only be prescribed by a psychiatrist.

Psychosis of Parkinson's disease (PD): Paranoid ideations, hallucinations (visual and auditory) or delusions occur in approximately 50% of people with PD over the course of the illness. Currently it is believed that psychosis is an integral part of the disease. Clozapine was first introduced to treat this type of psychosis.

Prior to the clozapine era, treatment strategy leaned on reduction of dopamine therapy via use of 1st generation antipsychotics. The drawback here was a worsening of motor function. Therefore 2nd generation antipsychotics supplanted these conventional agents. Among these 2nd generation drugs in addition to clozapine, QTP, ziprasidone, aripiprazole or paliperidone have been in use to combat this neuropsychiatric morbidity. Clozapine or QTP have been mostly used. All these 2nd generation agents have their side effects, the worst of which are the metabolic and sedative ones that are a real disadvantage, especially in the geriatric age group. Such undesired effects are very typical for QTP, making clozapine the best choice for the treatment of psychiatric (symptoms and signs) elements of this neuropsychiatric morbidity [40], unless there is an obvious contraindication to its prescription. Polypharmacy in PD is an inevitable situation, such that in order to avoid drug interactions QTP should not be recommended in PD.

Others

Tourette syndrome: Pharmacological intervention should be kept for treatment of severe symptoms only. Atypical antipsychotics with a low incidence of extrapyramidal side effects such as QTP and clozapine have been used successfully to treat the symptoms of Tourette's syndrome. With low doses of QTP, the side effects will be minimal. It is believed that the efficacy of QTP and other 2nd generation antipsychotics to treat tics is to lower D₂ site occupancy. It has also been hypothesized that tic individuals are D₂ sensitive and need lower doses of medications. It seems that QTP is a good choice with respect to treatment of symptoms of Tourette's syndrome, but the drawback again, according to a retrospective case-note study, is weight gain [41]. One should try small doses of this agent, even though sedation and weight gain go hand in hand as the greatest drawback when using this atypical antipsychotic agent.

Musical hallucination: Is a rare sort of auditory hallucination which describes a disorder where sound in the form of instrumental music, orchestral works, religious pieces, or favorite popular songs from the media is problematical. Before commencement of treatment, one must evaluate two important things: firstly, the response to non-pharmacological treatments, and secondly the effects of this morbidity on the patient's quality of life. Optimal drug treatment should target the etiological type of morbidity [42], which are the following: hypoacusis (impaired hearing), psychiatric (schizophrenia and psychosis), focal brain lesion (auditory cortex, pons), (sensory cortex reticular formation) resultant of encephalitis, epilepsy and intoxication (drugs and psychedelic agents). Low doses of QTP is a good choice to treat bedtime (hypnagogic) musical hallucination [43]. Quetiapine has also proven to be a good option as a rapid and effective form of treatment against resistant auditory hallucinations of schizophrenia. This was demonstrated in a case report that included two patients. The same study also showed QTP to be effective in the improvement of cognitive impairment in schizophrenic patients [44]. In recent psychiatric practice the drug of choice to combat treatment-resistant schizophrenia is clozapine, because this is a more potent antipsychotic than QTP and has a narrower side effect spectrum [45].

Restless leg syndrome (RLS): Quetiapine has been one of the good alternatives in the treatment of RLS, although sometimes QTP itself can be the predisposing factor behind the development of this syndrome [46]. Again, this reflects the fact that we do not know precisely how QTP can cause these two opposite effects. It could, however, be a result of dose dependent reactions, as is the case in sedation.

Pharmacopoeia of quetiapine: Quetiapine is manufactured and marketed for oral administration as quetiapine fumarate in oral suspension and as tablets. Available tablets contain doses of 25 mg, 50 mg, 100 mg and 200 mg, and capsule-shaped tablets with a content of 300 mg or 400 mg. Ferric oxides are added to color these preparations in order to make it easy to discriminate between different doses of these tablets and capsules. These oral preparations also contain inactive materials to make them easier to swallow. Sustained-release (extended-release) or depot tablets are also available as Seroquel XL and Seroquel XR, both for treating schizophrenia as well as maintenance therapy for this disease. These depot preparations have also a place in treatment of bipolar depression where prolonged antipsychotic therapy is indicated. To our knowledge, there exist no parenteral preparations of this agent, neither long-acting lipophilic preparations for i.m. use, nor hydrophilic i.v. preparations.

Titration of quetiapine dose in adults

Acute schizophrenia: One should start with 300 mg/day, with a daily increment of 300 mg to reach a dose of 400 - 800 mg/day. The maximum dose should not exceed 800 mg/day. This is the guideline for QTP to be used as a monotherapy. One should avoid as much as possible the combination of QTP with other antipsychotics and/or psychotropics to evade unexpected side effects that might occur because of potential drug interactions.

Maintenance dose in schizophrenia: Again, as monotherapy, for reasons mentioned above, the dose should lie somewhere between 400 - 800 mg/day and the maximum daily dose should not exceed 800 mg.

Bipolar I disorder (manic or mixed): Monotherapy or adjunct to lithium or divalproex (sodium valproate + valproic acid). Titration starts with 300 mg first day, second day 600 mg, day three 400 - 800 mg. This is also the recommended maintenance dose, and again the maximum daily dose here should not exceed 800 mg.

Bipolar disorder (depressive episode): As monotherapy, the titration should start with 50 mg 1st day, 100 mg 2nd day, 200 mg 3rd day, and 300 mg 4th day. The recommended daily dose is 300 mg, and the maximum should not exceed this.

Major depressive disorder (adjunct with antidepressants): 1st day 50 mg, 2nd day 100 mg, 3rd 150 mg. The recommended daily dose should lie between 150 - 300 mg, and the maximum daily dose is 300 mg. These dosages, however, might vary from one center to another according to: I. Experience psychiatrists have themselves with this drug. II. The importance of taking into consideration possible interactions QTP might make with other psychotropics, and/or with drugs of other pharmacological categories, because of other concomitant morbidities that patients might have (as is the case with geriatric patients). One thing worthy of mention in this context is that the titration of the daily dose of QTP is not proportional to its serum level. Indeed, dosage is often dependent mainly on the experience of a given psychiatrist, or on the guidelines adopted by different centers.

Serum therapeutic and toxic levels of quetiapine

Determination of therapeutic serum levels of antipsychotic drugs is sometimes needed for titration of their daily doses, and both the age and gender of a patient has a lot to say in this respect. For QTP this will not be very helpful (as stated above), because titration of therapeutic daily doses of QTP will not be reflected by its serum level, in other words, regarding this agent, these two parameters correlate weakly [47]. In a study on schizophrenic patients being treated with QTP, it was again found that there is a poor relationship between daily therapeutic dose and plasma QTP concentration. This is probably attributed to: I. The short plasma half-life of the drug, II. The serum level of QTP indeed reflects other parameters, such as adherence of the drug and measurement of metabolites of QTP, which are many, but only one is active (N-desalkylquetiapine). The accumulative daily doses of QTP itself may enhance the value of the therapeutic serum level of the drug [48]. Determination of serum QTP levels might help the investigation of suspected cases of acute poisoning. ARUP labo-

ratories in New York (US), have suggested two draws to determine serum quetiapine levels, which were detected by Quantitative Liquid Chromatography-Tandem Mass Spectroscopy techniques and these are:

- Predose draw, 70 - 170 ng/ml as the therapeutic range, and > 1000 ng/ml as the toxic range, these values are the ones that are recommended.
- Peak draw, measured after 90 minutes post dose, where the therapeutic range is 100 - 1000 ng/ml, and toxic values are > 1500ng/ml. The Department of Health (DOH) in New York State, has suggested these values but these have not yet been validated. The University of Iowa has accepted these values for serum QTP levels, and they appear in their Handbook of Pathology. One thing should be made clear i.e. these values are not intended to be the sole diagnostic factor related to patient management.

Quetiapine in pregnancy and breast feeding

To date, no definitive association has been found between use of antipsychotics during pregnancy and an increased risk of birth defects or other undesired outcome. However, there is a paucity of information, with a lack of large, well-designed, prospective comparative studies. The information presented here should therefore not be interpreted as conclusive about the safety of these drugs, since more research is needed. Women who require treatment should always discuss the risks and benefits of pharmacotherapy with their physician and, if it is felt that treatment should be continued during pregnancy, the evidence-based information presented here should be of help when having to make an important decision. Teratogenesis associated with the use of antipsychotic agents is generally unknown [49]. There is no clear evidence indicating that QTP is teratogenic in humans. This is attributed to the very limited experience we have regarding use of atypical antipsychotics during pregnancy in humans.

The general clinical guidelines that are accepted among clinicians (psychiatrists, obstetricians and pediatricians) and antenatal maternal-infant care givers, concerning pregnancy and breastfeeding for those who are on antipsychotics, are the following:

- Firstly, serious evaluation of the risk/benefit ratio of fetal and neonatal drug exposure.
- Secondly, severity of maternal psychiatric illness.
- Thirdly, careful choice of the appropriate agent that possesses a balanced safety/efficacy profile [50].

Concerning QTP, this atypical (2nd generation) agent is categorized in group C by the Australian Therapeutic Goods Administration (AUTGA). The agent has also been classified into group C by the US FDA (pregnancy category). Group C drugs are those, according to their pharmacological effects, that have caused or are suspected to induce harmful effects on the human fetus or neonate, and which may be reversible without causing any malformation. These conditions include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in such neonates.

Neonates exposed to antipsychotic agents within the third trimester of the pregnancy are at risk of developing extrapyramidal neurological disturbances, withdrawal symptoms, prematurity, low or high birth weight (neonates) and gestational diabetes (pregnant women) [51]. Females who are within childbearing years of age have to notify their physician if they are pregnant or have a plan to become so during treatment with QTP.

In the limited published human data, there are no reports indicating major malformations associated with use of QTP during pregnancy. There is no or very limited controlled data in human pregnancy [52]. Reports on potential complications, which have varied in severity,

are very few. In some cases, symptoms have been self-limited, in other cases neonates have required support at an intensive care unit and needed hospitalization. Quetiapine is only recommended for use during pregnancy when there are no alternatives and benefits outweigh risk. Because of inadequate folate intake among obese women taking atypical antipsychotics, there may be a high risk of developing neural tube defects thus a supplement of folic acid (4 mg/day) has been recommended. There is always controversy where it is stated that QTP therapy during pregnancy does not carry potential risk for the development of major congenital malformations [53,54].

There is a high correlation between concentrations of the drug in maternal serum and umbilical cord blood (amniotic fluid). In such a vulnerable population it is important to monitor the therapeutic serum levels of QTP to minimize the passage of this agent to the fetus [55].

Breastfeeding: Broadly speaking, mothers who are on QTP therapy should be discouraged from breastfeeding, simply because the drug is secreted in breast milk. Most of the studies in this respect are built on results from a limited number of breast-fed infants exposed to antipsychotics via mother's milk.

Indeed, there is no firm and evidence-based data for the safety of such a nursing routine. Counseling of breastfeeding mothers should be carefully assessed by both a psychiatrist and a pediatrician. Care providers should consider the following: pharmacokinetics of the given drug, disease severity, psychosocial options (alternative therapy measures), preventive interventions and make an evaluation of the possibility of discontinuing breastfeeding completely, and the consequences of the latter on maternal-infant relationships. If an antipsychotic is absolutely indicated for a breastfeeding mother who suffers bipolar depression, QTP or olanzapine should be evaluated as first-line choices of treatment [56,57].

Limited long-term follow-up of infants exposed to this drug during breastfeeding have generally shown that they exhibit normal development. However, due to the potential for serious adverse reactions in nursing infants and a lack of robust data, a decision should be made to discontinue breastfeeding or discontinue use of the drug, having considered the importance of the drug to the mother. If a mother must use QTP then the infants' developmental milestones should be monitored. In other words, the use of the drug may only be justified if the potential benefits outweigh the potential risk to the fetus.

Pediatric uses of quetiapine

Quetiapine has been used for treatment of different psychotic and non-psychotic disorders in children and adolescents. Different types of statistic studies suggest that QTP may be a promising agent with a potential for use in young patients suffering from a spectrum of conditions varying from psychotic disorders including psychosis, bipolar disorders, conduct disorders, autism spectrum disorders, Tourette's syndrome and personality disorders. First in 2009 was the use of QTP approved by the FDA for treatment of schizophrenia and bipolar depression. The resulting outcome of approval has established that the drug is well tolerated both in pediatric and adolescent populations during short courses of therapy (acute psychosis and intermediate maintenance therapy). Studies have also elucidated that hyperprolactinemia and EPS side effects are low when QTP is used, in comparison to other antipsychotics. The prominent problem with this antipsychotic agent is weight gain, accompanied by disturbances in lipid profile, in other words the complications of metabolic syndrome. Lipid profile and blood glucose need to be carefully monitored. The outcome/risk ratio during prolonged treatment needs to be determined by performing further studies [58]. Taken together there is a lot of controversy about the metabolic complications of QTP as discussed elsewhere in this work.

Guidelines for titration of quetiapine doses for use in adolescent and pediatric cases:

- To treat schizophrenia in adolescents (13 - 17 years), the recommended daily dose is (400 - 800 mg) and the maximum daily

dosage should not exceed 800 mg. With a gradual daily increase, the starting dose is 50 mg (1st day), and then 100 mg (2nd day), 200 mg (3rd day), 300 mg (4th day) and 400 mg (5th day) and so on.

- To treat bipolar I disorder (acute manic phase), in children and adolescent patients, as monotherapy, the recommended daily dose should lie between 400 - 600 mg, and the maximum daily dose should not exceed 600 mg. Again, the dose should be titrated by gradual daily increment, in exactly the same way as for treating schizophrenia. The gradual increase is important and especially so in this age group of patients, because you never can be sure how these individuals will react to a 2nd generation antipsychotic. In addition to the metabolic side effects of this agent (in the case of prolonged use as maintenance dose). The risk of suicide [59,60] and hypertension should be seriously taken in consideration. For side effects of QTP see table 1.
- ADHD and Autistic Spectrum Diseases (ASD): A case report from Kuwait advises use of a relatively low dose of QTP (300 mg/day) as an add-on to stimulants. Stimulants, however, have their own drawbacks such as insomnia, weight loss and hypertension. In pediatric cases use of QTP, especially in low doses, is regarded as safe and might augment the action of stimulants in treatment of ADHD [61]. Short-term low-dose QTP treatment may reduce aggression levels and improve sleep quality in adolescents with ASD [62].

Acute poisoning with quetiapine

Very common side effects				
1. Anticholinergic: Dry mouth				
2. CNS: Dizziness, Headache, Somnolence (drowsiness)				
Common side effects				
Cardiovascular	Gastrointestinal	Metabolic	Neurological	Allergic reactions
Tachycardia	Dysphagia	Hyperlipidemia	Agitation Insomnia	Drug induced
Hypertension (children, adolescents)	Dyspepsia	Weight gain	Tremor (EPS)	Allergic rhinitis
Orthostatic hypotension	Pharyngitis	Elevated liver enzymes	Lethargy (fatigue)	
Peripheral edema	Polyphagia		Asthenia (weakness)	
	Vomiting		Hyperalgesia (Pain)	
	Constipation		Backache	
	Abdominal pain			
Infrequent (rare side effects)				
Cardiovascular	Metabolic	Hematologic	Neurological	Inflammatory
Prolonged QT interval	DKA*	Agranulocytosis	Seizures	Pancreatitis
Syncope	Hyperlipidemia	Thrombocytopenia	NMS*	Myocarditis
Cardiac arrest	Hyponatremia	Venous Thromboembolism	Tardive dyskinesia	Hepatitis
	Jaundice	Leucopenia	Priapism	Thyroiditis
	Hypothyroidism	Neutropenia	Restless leg syndrome	Rhabdomyolysis
	Galactorrhea	Eosinophilia		Anaphylaxis
	Gynecomastia			SJS ^o
	Abnormal menses			

Table 1: Side effects of Quetiapine.

Abbreviations: DKA*: Diabetic Ketoacidosis; NMS*: Neuroleptic Malignant Syndrome; SJS^o: Steven Johnson Syndrome.

Suicide attempts (poisoning) using an overdose of QTP are extremely rare in clinical practice. Acute toxicity caused by an overdose is possible in psychotic, major depressive disorder, and in patients with borderline personality disorder [63]. The common reasons behind such tragedies are the following: self-adjustment of medications or irregular medication compliance, dehydration (lack of self-esteem), coexisting cardiac pathology such as dysrhythmia, interaction with concomitant drugs because of other pathologies. If such a case is not rigorously treated, then rhabdomyolysis can develop, and the possibility of mortality will increase immensely if neuroleptic malignant syndrome (NMS) is coexistent. One should be cautious here because the clinical picture could be like that of tricyclic antidepressant poisoning.

The clinical manifestations of acute QTP poisoning depend on the amount taken and age of the patient. In this regard there is individual variation in the symptoms and signs manifested among different groups of patients.

The pharmacological effects of QTP are primarily exerted via antagonism of serotonergic (5-HT₂) and dopaminergic (D₂) receptors.

Serious poisoning can be expected in adults when the dose taken is more than 5 gm.

Signs and symptoms are:

- Dizziness, nausea, agitation, memory impairment, confusion, hallucination and general CNS-depression.
- Tachycardia, hemodynamic instability, hypotension, QT-interval prolongation [64] ectopic ventricular beats (EVB) and atrioventricular type of heart block.
- Respiratory depression (hypoventilation): Slow, shallow breathing, hypercapnia, hypooxygenemia.
- Muscle cramps, and extrapyramidal symptoms (EPS).
- Electrolyte disturbances: Hypokalemia, hyponatremia.
- Anticholinergic symptoms: Dry mouth, constipation, sedation, blurred vision, urine retention.

Management: As in the case of NMS, it is best to treat cases of serious poisoning in a fully equipped ICU, for two important reasons, firstly: a ventilator, continuous EKG monitoring and well-trained intensive care medics are always available in such units and secondly there is possibility of deterioration of the condition and development of NMS. It will be therefore wise to admit this group of patients to an ICU [65].

- An open intravenous pathway (i.v. cannula) should be set up immediately in such patients, since circulatory collapse can occur making it then difficult to find obvious veins. It is thus important to avoid venous cut-down, and imperative to start i.v. administration of fluids. Since such patients are dehydrated, rehydration will also regulate their temperature.
- If one is fortunate enough to catch the patient within the first two hours of intoxication, gastric lavage with activated charcoal might be indicated [66].
- Arterial blood gas analysis should be performed and partial O₂ pressure, HCO₃ levels, and blood pH levels measured in order to detect metabolic acidosis.
- Intubation for ventilation and airway protection is important in comatose patients, thereby protecting the patient from aspira-

tion pneumonia (Mendelson's syndrome).

- Biperiden lactate (akineton) might be indicated to counteract EPS, but not in tardive dyskinesia [67]. Depending on the patient's condition, it is either administered orally, or parenterally (i.v. or i.m.) in comatose patients. The lactate form of this agent will also act as a buffer solution to modify metabolic acidosis that can be seen in such cases of toxicity.
- Some intensive care units also suggest the use of intralipid (intravenous lipid) to treat QTP poisoning immediately after performing gastric lavage. This can be lifesaving and function as a complimentary measure to others mentioned above [68].

Interactions of quetiapine with other drugs

Side effects of QTP are not only attributed to the drug *per se*, but also because of extensive interactions this psychotropic agent can be involved in when coincidentally administered with other agents and/or drugs from other categories. Polypharmacy should be generally avoided whenever possible, and especially when using other drugs that act on the CNS, i.e. psychotropics and those employed to treat neurological pathologies. Corner books of pharmacology, pharmacopeia [69] and websites of drug databases (e.g. drugs.com) show the very wide spectrum of interactions that QTP can enter with drugs from different therapeutic categories. A total of 1163 drugs are known to interact with this dibenzothiazepine derivative.

Major, moderate and minor interactions number 251, 897, and 12, respectively (drugs.com). To mention all the different types of interaction reactions is not within the scope of this review. One can conclude, therefore, that the side effects of QTP act like a double-edged sword, based firstly on the actions of the drug itself [70] and secondly based on its widespread nature of interaction producing complications when prescribed together with other drugs. There exists evidence showing that drug interactions can also be attributed to an unhealthy diet that contains bacterial lipopolysaccharides. It is believed that this type of diet down regulates anti-aging genes that are relevant to mitophagy and hepatic amyloid beta. Caffeine consumption, with its consequent interference on amyloid beta/drug brain to liver transport, decreases the capacity of hepatic drug metabolism. On the other hand, healthy diets that activate anti-aging genes are necessary to prevent drug-drug interactions [71]. A healthy diet also averts drug induced mitochondrial dysfunction, in other words precluding certain mitochondrial diseases such as insulin resistance and non-alcoholic fatty liver disease. These morbidities are among well-known contributory factors to the induction of drug-drug interaction [72]. None of the psychotropic agents currently in use have selective actions on their receptors, and polypharmacy cannot be avoided, especially in patients of the geriatric age group, where coexistence of many diseases is possible [73,74]. One must double check and act wisely when deciding to prescribe QTP together with other drugs that act on the CNS. Quetiapine interacts with almost all known psychotropic and all CNS drugs. It also reacts with drugs that act on the cardiovascular system and those employed in treatment of metabolic diseases, such as antidiabetic agents. Concerning diseases of metabolic syndrome e.g. type II diabetes, QTP can influence the disease and counteract the action of metformin. It is not known how this antipsychotic agent operates at the cellular level, and the list of complications that this antipsychotic agent is involved in is still increasing. Recently, cases of drug-induced cataract formation following use of this agent have been reported, and this phenomenon was also observed in animal studies a decade ago [75]. One must have an absolute indication to prescribe QTP to patients, especially when it is to be coadministered with other psychotropic agents, and other alternatives should therefore be evaluated whenever possible.

Quetiapine dependence

Family doctors and general practitioners should consult with psychiatrists when deciding to reduce or discontinue psychotropic agents, generally including QTP. This is especially important when QTP is used as an antidepressant and or anxiolytic (hypnotic). Quetiapine can indeed permeate through the cell membrane (but not as readily as benzodiazepines do), pass into the cytoplasm, bind to nuclear receptors and ultimately influence the cell cycle. This fact has been proven in *in vitro* rat oligodendrocytes [76]. A Langmuir lipid monolayer study has shown that QTP does not increase the surface area as much as chlorpromazine, pimozide or trifluoperazine, in other

words it intercalates less than the previously mentioned antipsychotics in the inner leaflets of membrane phospholipid bilayers [77]. Results from some animal studies have demonstrated that QTP can cause drug dependence [78]. In that respect development of drug dependence is possible.

There are no clear examples from human studies that this drug causes dependence, on the contrary it might play a role similar to that of methadone in treatment of opiate addiction. There are promising results although they are preliminary that treatment with 300 mg of QTP was tolerated by cannabis-dependent patients and associated with decreased cannabis use [79].

There are also case reports on QTP abuse and dependence, particularly among patients diagnosed with substance abuse. Some of these patients in this group also use the drug intranasally and intravenously. In some cases QTP is combined with other substances, such as cocaine or marijuana, to increase sedation. It is believed that the anxiolytic sedative action of the drug lies behind this kind of abuse [80]. One has to mention here that there exists no major study proving that QTP is an addictive drug. Patients with a drug abuse history need to be kept under close observation in order to pick up any sign of misuse of QTP. In other words, it is important to recognize development of tolerance that may occur as a result of dose increment, alternately observe any form of abnormal behavior associated with a drug seeking pattern [81].

Quetiapine withdrawal syndrome

The signs and symptoms of antipsychotic drug withdrawal generally include nervousness, anxiety, insomnia, light headedness, headache, dizziness, nausea, vomiting, diaphoresis (excessive sweating), tachycardia, orthostatic hypotension. Some psychiatrists also add dyskinesia and psychosis to withdrawal syndrome as rebound effects resultant of high-level sensitivity of the dopaminergic receptors to neuroleptic therapy.

The syndrome develops usually, but not always, in individuals (patients) as a result of reduced reaction to the drug following its repeated use, a condition known as “drug tolerance”. The consequence of which is to increase the dose in a hope of re-amplifying (augmenting) the effects of the drug. Unfortunately, this does not occur, and may indeed intensify the level of drug tolerance. The two terms (withdrawal syndrome and drug tolerance) are related but not necessarily always associated with one another. In other words, drug addiction that causes withdrawal syndrome is not the other face of drug tolerance, because drug tolerance is a reversible condition (drug holiday, stopping the taking of a drug for a period). In clinical practice many drugs should not be stopped abruptly, especially those agents that can induce dependence (tolerance). These include to a certain extent also drugs used in treatment of some somatic morbidities such as diabetes, asthma, cardiovascular, and neurological disorders. Neuroleptic drugs should never be stopped abruptly. In addition to drug withdrawal syndrome (because of the drug *per se*), the other problem here is that of relapse and a re-flourishing of symptoms and signs of the primary psychiatric morbidity that these drugs were prescribed for (i.e. a relapse). These might be even stronger and make it more difficult to treat the ailment due to refractoriness to antipsychotic therapy. In pharmacological terminology this is known as the rebound effect. A relapse, where the symptoms and signs of depression occur, for example because of abruptly stopping use of antidepressants (SSRI) might be dangerous and may carry a risk of suicide [82]. The same thing might be also true for hypnotics (anxiolytics) and furthermore, antipsychotics. Under such circumstance’s psychiatrists may need to switch to another class of psychotropic agents. The worst scenario is to commence with combination therapy because one must bear in mind the consequences of drug interactions etc. The above-mentioned is true for QTP withdrawal [83], although to a lesser extent than 1st generation antipsychotics.

These problems are indeed a disadvantage for almost all currently known psychotropics, including QTP. Basically, our knowledge concerning QTP withdrawal syndrome is poor although there is some documentation that eludes to withdrawal manifestations of QTP discontinuation [84]. But because the drug causes sedation and somnolence (as a side effect or off-label use), it is quite possible to cause withdrawal syndrome when dosage is abruptly reduced [85].

Many drug foundations, including the British National Formulary (BNF), recommend gradual tapering in order to discontinue use of antipsychotics. This is to avoid occurrence of the above-mentioned unwanted and (sometimes) dangerous syndrome. Basically psychotropics (antipsychotics, antidepressants and hypnotics) induce changes at dopamine, serotonin, adrenergic and histamine receptor sites in the human brain. It is highly expected, therefore, that one will come face to face with withdrawal syndrome when the drug is abruptly discontinued or hurriedly tapered in dosage. What makes things worse is that to our knowledge there are no specific guidelines with documented efficacy, or safety protocols accepted by major psychiatric centers on a global basis, concerning exactly this serious issue. Clinical experience is the only guiding tool in this aspect.

Suicide because of quetiapine use and/or abuse

Patients with psychiatric diseases such as psychosis, bipolar disorder and depression are liable to terminate their lives by committing suicide. Drug abuse, especially when combined with alcoholism, is also one of the known factors leading to suicide.

There is no clear evidence that QTP, as monotherapy, can cause suicide as an emergent side effect of therapy. Data from the FDA (April 2018) shows that female patients, aged 40 - 49, using QTP concomitantly with olanzapine, sertraline, risperidone, clonazepam or alprazolam (short acting benzodiazepines) are liable to commit suicide. This could be resultant of interactions of QTP with concomitantly used psychotropics (mentioned above), or side effects of these individual psychotropic agents *per se*, although it is difficult to be 100% certain regarding this point.

On the contrary, it is believed that QTP reduces suicidal risk in agitated depressive patients. According to Weisler, *et al.* therapy with slow release tablets of QTP cause no increment in risk possibility of treatment-emergent suicide in patients with major depressive disorder, if they are not otherwise judged to be in a high suicide risk category [86]. The situation, however, might be different in children, adolescents or young adults. Quetiapine is not approved for use in patients under the age of ten years.

Contraindications of use of quetiapine

Absolute contraindications are:

- Hypersensitivity to the drug or its components
- Concomitant use with CYP3A4 inhibitors such as: HIV Protease inhibitors, antifungal agents of azole type, antibacterial (erythromycin, clarithromycin) and an atypical antidepressant nefazodone (currently not in common use).
- Relative contraindications of QTP use are shown in table 2.
- Caution should be taken when prescribing QTP to the following groups of patients:
 - Major depressive disorder
 - Patients younger than 25 years
 - Pregnancy 3rd trimester
 - Elderly patients (especially those with dementia-related psychosis)
 - Breast cancer patients on cytotoxic drugs
 - High body temperature, since it can cause neuroleptic malignant syndrome.

1	Metabolic and Electrolytes	<p>Diabetes, hyperglycemia, obesity.</p> <p>Hypothyroidism</p> <p>Hyperlipidemia</p> <p>Liver diseases</p> <p>Hyperprolactinemia</p> <p>Cataracts</p> <p>Hyponatremia</p> <p>Hypokalemia</p> <p>Hypomagnesemia</p>
2	Cardiovascular	<p>Ischemic heart diseases: infarction, angina pectoris</p> <p>Hypertension</p> <p>Torsade's de pointes</p> <p>Prolonged QT interval</p> <p>Arrhythmia (tachycardia, bradycardia)</p> <p>Postural hypotension</p> <p>Chronic heart failure (congestive)</p>
3	Hematologic	<p>Hypovolemia</p> <p>Anemia</p> <p>Leukopenia</p> <p>Agranulocytosis</p> <p>Neutropenia</p>
4	Neurologic	<p>Neuroleptic malignant syndrome</p> <p>Epilepsy, low seizure threshold</p> <p>Cerebral artery stenosis</p> <p>Dementia (elderly patients).</p> <p>Hyperkinetic movement disorders such as: ataxia, chorea, dystonia, hemifacial spasm, Huntington's disease, myoclonus, restless legs syndrome, Tics (Tourette's syndrome), tremors, Wilson's disease</p> <p>Tardive dystonia (drug induced)</p> <p>Tardive dyskinesia (drug induced)</p>
5	Psychiatric	<p>Confused patients</p> <p>Dementia related psychosis</p> <p>Thoughts of suicide</p>

Table 2: Relative contraindications of quetiapine.

Receptor types/subtypes with which quetiapine can interact

Quetiapine has a very broad spectrum of receptor types/subtypes to which it can interact with and thereby elicit many irrelevant pharmacological actions. The following are most well-known receptors studied:

- Being an antipsychotic agent, QTP acts on dopamine receptor subtypes (D_1 , D_2 , D_3 , D_4 and D_5), functioning as a dopamine receptor antagonist.
- Serotonin receptor subtypes (5-HT_{2A} , 5-HT_{2B} , 5-HT_{2C} , 5-HT_3 , 5-HT_6 and 5-HT_7), operating as an antagonist. It also acts as a partial agonist on the 5-HT_{1A} receptor. It has not been determined whether QTP can act on 5-HT_{1B} , 5-HT_{1D} , 5-HT_{1E} and 5-HT_{1F} receptor subtypes.
- Histamine antagonist on the subtype H_1 .
- Acetylcholine receptor antagonist to muscarinic action: receptor subtypes M_1 , M_3 , and M_5 .
- Adrenergic receptor antagonist, both α_1 and α_2 and their subtypes.

It is worthy of mention that QTP affects also the following, although at very different levels of potency: SERT and NET, as a blocker, that is as an antagonist. NMDA (PCP) as an antagonist. It has not yet been determined whether QTP acts on VGCC, DAT or hERG receptors [87,88].

It is clear that the potential of QTP to interact with all these receptors and/or subtypes makes it a very nonselective psychotropic agent and this gives an indication as to why it has such a broad profile of side effects.

Discussion

It is clear from what has been stated hitherto, that QTP not only has antipsychotic effects but also mood-altering effects. It has clear and well-recognized use in treatment of unipolar, and the exacerbations of bipolar depressive disorder. Mood elevation caused by this agent is actually attributed to its active metabolite norquetiapine (N-desalkylquetiapine). The metabolite activates the ERK/MAPK signaling pathway that releases GDNF (Glial cell Derived Neurotrophic Factor), and this pathway has been proposed to be specific for antidepressant agents including QTP, where they exert their therapeutic action [89].

Titration of the optimal dose should be perfectly balanced, because QTP can elevate the mood of an individual to an uncontrollable height and this might induce mania. A case report on three psychotic patients, who received (300 - 800 mg QTP), developed mania. In two of these three patients' manic symptoms subsided after withdrawal of QTP and its substitution with sodium valproate. The third patient continued with QTP, with an addition of zuclopenthixol (1st generation antipsychotic agent) as an add-on antipsychotic agent [90]. The antidepressant property of QTP has a tremendous advantage when treating psychotic patients that have a depressive mood in addition to their major psychotic morbidity, namely schizophrenia [91]. Depression coincident with psychosis is very common, and psychotic individuals do not realize that they are. The prescription of QTP might be a good choice in patients of this category. Post psychotic depression is another good indication for this medication [92].

When we take into consideration all that has been said up to now about the clinical uses of QTP, one can conclude that this psychotropic agent is like a magic wand since it can be used to treat almost all psychiatric, and many neurological diseases. Is QTP the real magic wand we are looking for? Most likely the answer would be negative.

Another question we need to ask ourselves: is QTP a potent antipsychotic? The answer here is no. It is not potent based on its low affinity for dopamine receptors, thus it has very low EPS [93]. It is true that protein binding of a given drug reflects to a certain extent its therapeutic potency, and QTP possesses this property (see elsewhere in this review). Indeed, this property is not the only parameter that determines the therapeutic potency of a given drug. This factor can be true provided the other pharmacokinetic parameters are constant, such as: half-life, solubility, metabolic pathways, active metabolites of the agent, etc. It is rather the efficacy of the agent regarding activation of its target receptors when it has become attached [94].

Concerning dosage, the daily therapeutic dose of QTP for treating psychosis lies somewhere between 300 - 800 mg. On the other hand, the daily dose of olanzapine, for example, is 15 - 30 mg, even though it is much more potent than QTP. Another example is the daily dose of the 1st generation antipsychotic haloperidol, which is as low as 2 - 20 mg, yet it is a potent antipsychotic [95]. A further example of differences in dosage is the conventional (1st generation) antipsychotic chlorpromazine, where its common daily therapeutic daily dose is 100 - 600 mg, again it is not a potent agent.

Quetiapine is not superior to 1st generation (typical) antipsychotic agents in treatment of the negative symptoms of schizophrenia [96]. One of the pivotal facts concerning 2nd generation antipsychotics is that they cause less sedation, an important factor regarding schizophrenic patients in relation to deinstitutionalization and aiding them to re-integrate into society. The latter is attributed to the low level of affinity toward the histamine H₁ receptor; indeed, this is an advantage of QTP. It is worthy of mention that haloperidol, a 1st generation antipsychotic, has the least sedative action of almost all known antipsychotics, although it has a very wide spectrum of side effects [45]. It is true that QTP causes less sedation, but in the meantime this agent, as off-label use (in low doses), is prescribed to induce insomnia [97]. This controversy indeed reflects the fact that we do not yet know how these drugs exactly exert their pharmacological functions, at least at the neuronal level. Quetiapine binds to different types of receptors, either agonizing or antagonizing actions of the neurotransmitters, which naturally attach to these receptors to fire the signal transduction cascade. Quetiapine might affect these receptors through a modulation of their spatial alignments by intercalating between the phospholipid molecules of the inner leaflets of neuronal membranes, and thus change membrane curvature. This would in turn affect substrate availability to membrane-associated enzymes involved in signal transduction in such a way that the intracellular response would be altered [98,99]. Psychotropic agents including QTP are cationic amphiphilic molecules composed of two moieties (hydrophilic and lipophilic), for structures see figure 1.

Lipophilic moieties intercalate in-between the phospholipid molecules and push them apart, thus changing the alignment of different integral receptor proteins studded in the neuronal membrane [99,100]. Logically it does not make sense that QTP molecules bind to many different types (and subtypes) of receptors, where they agonize some and antagonize others. When so doing, however, QTP almost paralyzes the neurons, as is the case with almost all known antipsychotics, such that one can perceive that these agents perform a sort of drug-induced (chemical) lobotomy. Although there must be other explanations for this phenomenon, the intercalation theory [101] would seem to be a plausible one.

Another devastating drawback of QTP is that it causes neuroleptic malignant syndrome as observed with other 1st and 2nd generation antipsychotics [102].

According to a case report, QTP even at a low dose of 100mg daily, caused galactorrhoea [103]. Further, a new case report has demonstrated that QTP can cause hyperprolactinemia and amenorrhoea [104]. So QTP might be superior to 1st generation (conventional) antipsychotics only because of its off-label use. QTP indeed is one of the xenobiotics that can induce changes in chromatin remodeling by modulating transcriptional regulatory factors associated with modification by histones, and thus cause epigenetic changes that affect certain genes. Among these is the sirtuin 1 gene (*Sirt1*) that encodes the nuclear receptor protein sirtuin 1. Abnormal synthesis of this receptor protein (which is calorie sensitive) because of a defective (*Sirt1*) gene, results in a disturbance in nutrient metabolism and contributes to insulin resistance, NAFLD (Non-alcoholic fatty liver disease), energy imbalance and circadian rhythm disorders [105]. This is one of the plausible explanations concerning how QTP can cause obesity and metabolic syndrome.

Similar to the 2nd generation agent clozapine, QTP releases reactive oxygen species (ROS), which are best known as free radicals. In biological units, these unstable molecular species with unpaired electrons, such as superoxide, hydrogen peroxide, and hydroxyl radicals, are commonly associated with cell damage. ROS can readily react with macromolecules of biological systems e.g. DNA, causing uncontrollable chain reactions that result in damage and thus can act as a teratogen in sensitive fetal tissues (inner cell mass of the embryo) and/or as a carcinogen in adults. In theory, accepted optimal antipsychotics should be devoid of this unwanted property, however, this is not the case [45]. This fact necessitates the oral administration of micronutrients, especially those that possess antioxidant properties such as vitamins C, A (citrus fruits and carrots) and E (different oils, milk, fish and nuts). Selenium-containing preparations are also beneficial e.g. tuna fish. Polyunsaturated fatty acids (PUFAs) are also pivotal for neuronal membrane integrity and important for their proper function. Fish, olives and leafy vegetables are good dietary sources for these essential fatty acids. One more important thing to add is that for therapeutic use QTP exists as a fumarate salt, see figure 1. This is probably to counteract the action of the release of ROS. Fumarate possesses an indirect antioxidant activity, where it activates the Nrf₂ antioxidant response pathway that neutralizes the cytotoxic effects of oxidative stress [106]. In addition, fumarate has biological significance in that it is an intermediate metabolite in a major metabolic pathway (citric acid cycle) and thus oxidative phosphorylation (biosynthesis of ATP). The 2nd generation antipsychotic agent clozapine also releases reactive oxygen species. ROS could in fact be one of the hidden reasons underlying the wide spectrum of side effects associated with many antipsychotics, such as QTP and clozapine. It is worthy of mention that the fumarate form of QTP enhances its absorption from the GIT.

Conclusion

All currently available antipsychotic agents, including QTP, are nonselective and show a broad spectrum of side effects. Work to find a drug for the radical treatment of psychosis needs to be performed in parallel with research to elucidate the real pathophysiology of psychoses at the neuronal level. Unfortunately, the lack of achievement over the long period of time that has lapsed since the earliest antipsychotic agents were introduced is not satisfying. This assertion is supported by the simple fact that currently there exists no radical treatment for psychoses. Antipsychotics have in fact a very wide spectrum of unwanted side effects. The most undesirable of which are the following: sedation, abnormal metabolic and endocrine changes (metabolic syndrome) and extrapyramidal side effects (EPS). Other serious side effects such as hepatic damage and blood dyscrasia are quite possible. Neuroleptic malignant syndrome is another life-threatening secondary effect caused by many drugs acting on the CNS and especially psychotropics.

Based on the above there were direct reasons for drug designers, especially those involved with molecular docking, to design the so called 2nd generation group of agents (atypical or nonconventional), of which QTP is one of them. In general, these agents are therapeutically more potent than many of the conventional ones, and cause less sedation, and probably also less EPS. But they also have their own drawbacks, since they are not identical in action, potency, or about side effects. Many of these 2nd generation agents release ROS and induce blood dyscrasia as an idiosyncratic reaction. Concerning QTP, it acts indeed like a conventional 1st generation agent [96]. It is not selective in action on a certain receptor type (or subtypes). It acts on a huge number of unrelated receptors thus it is not a potent antipsychotic. It releases ROS and thus it could be both teratogenic and carcinogenic, although currently there exists no solid evidence in humans to prove this. It can cause sudden death because of QT interval prolongation in cases of intoxication. This is quite feasible with this agent (highly therapeutic), especially when prescribed to schizophrenic patients outside institutions. The most negative factor regarding QTP is its involvement in a great number of cross-interaction reactions with other drugs from different categories, and especially those that act on the CNS, and especially psychotropics. At present it is not known exactly how 1st and 2nd generation antipsychotic agents, including QTP, operate at the neuronal level. Since the real pathophysiology behind psychosis is not yet elucidated, researchers will continue to strive to identify what we call the optimal antipsychotic [45]. None of the antipsychotics, neither 1st nor 2nd generation agents currently in use are identical with the optimal antipsychotic that we are looking for. Concerning QTP it will continue in the drug market only because of its off-label use where it is prescribed in low doses.

Conflicts of Interest

None.

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