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The Ideal Antipsychotic: Hybrid between Typical "Haloperidol" And the Atypical "Clozapine" Antipsychotic

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Abstract

The differences in types of psychoses, the suboptimal therapeutic response of psychotic individuals to antipsychotics, the variation of the therapeutic effects of the same antipsychotic on different individuals with the same disease, resistance to treatment, relapses despite completing a course of antipsychotic treatment, and the broad spectrum of side-effects of antipsychotics including the most recently designed ones, are pivotal factors necessitating the discovery of new antipsychotic agents. These should be therapeutically potent, efficient in monotherapy and devoid of known dangerous adverse effects that antipsychotics are blamed for. In this comparative review we elucidate two antipsychotic drugs, namely haloperidol and clozapine (typical and atypical antipsychotic agents, respectively) and discuss both their advantages and disadvantages. Because the pathogenesis of psychoses is not yet fully understood, and the prevention of psychoses is almost impossible rather being a myth, the search for the so called ideal, or the near-ideal, antipsychotic agent will continue. Based on this we propose the design of a "hybrid structure" having the desired properties of haloperidol and clozapine, with the intention being to find an optimal antipsychotic agent that exerts efficient therapeutic effects against both positive and negative symptoms of psychosis causing least possible side effects, such as in monotherapy.

Keywords: Antipsychotics; Psychosis; Schizophrenia; Hybrid structure; Haloperidol; Clozapine; Neuroleptic malignant syndrome; Extrapyramidal symptoms; Agranulocytosis; Diabetes type II

Abbreviations: CPZ: Chlorpromazine; HPD: Haloperidol; CLZ: Clozapine; EPS: Extrapyramidal symptoms; NMS: Neuroleptic Malignant Syndrome

Introduction

Psychosis and bipolar affective disorder are two broad major morbidities a psychiatrist faces in the clinic. Psychosis is a Greek word meaning abnormal mind, and by definition it is a mental state of "loss of contact with reality". A psychotic person has impaired cognition, experiences hallucinations of different types, most important of which are auditory and visual, they might also have delusions, and may behave violently. Schizophrenia is the major category of psychosis. The cognitive deficits that schizophrenic individuals suffer from are actually more serious than the positive or negative symptoms (according to many psychiatrists). This is simply because cognitive deficits impair daily functioning and contribute mostly to chronic disability and unemployment [1,2]. Dissimilar to the other psychotic symptoms, these deficits do not improve during periods of remission even with the use of the most recently designed antipsychotics [3]. Cognitive impairments are also associated with other psychiatric diseases such as major depressive disorder, which make these individuals much more isolated and hinder their integration and function in society [4-6].

The term "Schizophrenia" also originates from the Greek, meaning the "split mind", reflecting the clinical presentation of the ailment. In fact, the disease is so-called because it is characterized by thought breakdown associated with poor emotional responses (avolition). The disease is clinically manifested by common symptoms the most important of which are delusions in the form of paranoia, such as the hearing of voices/noises that do not actually exist, and a bizarre way of thinking which lacks emotion and motivation. Briefly, the key of diagnosis is usually dependent on the observation of the patient's behavior (reported by a chaperone), and the experience reported by the patient himself/herself.

Another category is bipolar affective disorder formerly known as manic depressive psychosis, where the person experiences a swinging pattern of mood alternating between euphoria and depression through hypomania and mania. During the phase of hypomania, individuals appear energetic and excitable and may in fact be highly productive. In the manic state individuals begin to behave unwisely and impulsively without thinking about the consequences of their deeds. They suffer insomnia and get the propensity of making poor decisions due to irrational ideas they make about the future and their surroundings, and they might even commit suicide [7].

Pharmaceutical chemists and antipsychotic drug designers have been trying to find an efficient remedy to alleviate the grave and embarrassing symptoms/signs of psychosis and bipolar disorder. This is because these two ailments are real burdens on individuals and additionally for the national economy and social safety in all nations. For example, by 2008 the sale of antipsychotic drugs in the USA was the highest selling class of drugs with annual revenue amounting to almost 14.6 billion US Dollars [8]. Great advances in psychiatric health care have been made since the synthesis of chlorpromazine in 1950 [9]. The significance of this agent is that it was the first drug developed with a specific antipsychotic action. This agent actually served as

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being the prototype for the phenothiazine class of drugs, which later grew to comprise several other agents. Many phenothiazine-based antipsychotic agents are still in clinical use in many countries especially as depot preparations; on the other hand some are not, such as trifluoperazine. This phenothiazine-derived antipsychotic has been withdrawn from the drug market in some countries, mainly because it causes a broad spectrum of side effects and exhibits suboptimal therapeutic efficacy [10].

Concerning atypical antipsychotics most of these were developed recently, although clozapine was discovered in the same era as the "typical" chlorpromazine. It was only introduced for clinical use at the beginning of the nineteen seventies. Both classes tend to block receptors of dopamine pathways in the brain, though it is believed that atypical agents also exert their effects via binding to serotonin receptors. Antipsychotics should be prescribed by psychiatrists in optimal doses, for an appropriate duration, according to the clinical need of the psychotic patient, because unbalanced (irrational) dosage reduction or a sudden arrest of the antipsychotic therapy before properly completing a course of therapy, can cause serious symptoms such as insomnia, agitation, motor disorders and a possible return of psychotic symptoms [11,12].

Psychotic symptoms, resultant of senile organic brain syndrome (dementia) in the geriatric age group, which include aggression and paranoid ideas and delusions, should not be routinely treated with antipsychotic agents. One should be careful with this issue in such a way that it should be kept as an option only for individuals with severe distress or for those who are at risk of harming themselves and/or others [13]. In the elderly, one should instead direct the form of therapy towards psychosocial interventions rather than using drug therapy [14].

Antipsychotics are also termed neuroleptics, and according to previous terminology also called major tranquilizers and ataractics. As a matter of fact, these terms nowadays are being abandoned in favor of use of antipsychotic, which describes the desired pharmacological effects of the drug or the purpose for which it is being used [15]. These drugs (antipsychotics) are a class of psychotropic remedies primarily used to treat symptoms of psychosis that include delusions, all types of hallucinations and disordered thoughts which flourish in schizophrenia and to a certain extent in bipolar disorders. Nowadays antipsychotics are also being increasingly used in the management of certain neurological disorders. Discovery of chlorpromazine in the 1950s, which is a phenothiazine, caused a real revolution in the treatment of schizophrenia. This major event led to greatly reduced use of restrain, seclusion and sedation in the management of agitated patients [16]. It is worth mentioning that the availability of antipsychotic drugs curtailed to a great extent the indiscriminate use of electroconvulsive therapy (ECT) and psychosurgery. Their therapeutic use was one of the pivotal driving forces that led to the deinstitutionalization of many psychotic patients and enabled them to lead near-normal lives. This was achieved by using depot preparations of antipsychotic remedies and evaluation and/or treatment in the outpatient department of a psychiatric institution.

It also opened the gates for research in psychopharmacology, the result of which was the development of antidepressants, anxiolytics, and the majority of other drugs currently used in the management of different psychiatric diseases. The first clinical prescription of CPZ was in 1952 by "Laborit H" to nonpsychotic, non-manic patients, where he noted that the drug induced a sort of indifference towards the events happening around the individual. Another group led by "Delay, J." prescribed the agent for agitation, while "Deniker P et al." used CPZ for treatment of psychosis [17].

Classification of Antipsychotic Agents

Psychopharmacologists have classified antipsychotic drugs into two major categories, conventional (typical) and non-conventional (atypical) agents. The two drugs we have chosen in this comparative review are haloperidol and clozapine. They belong to conventional and non-conventional groups of antipsychotic agents, respectively. According to the new classification method which applies the chemical structure of agents for the purpose of nomenclature, haloperidol and clozapine are classified as butyrophenone and dibenzodiazepine derivatives, respectively [18]. The chemical structures of drugs discussed are presented in Figure 1.

Another classification method categorizes the atypical antipsychotics according to their pharmacological properties, for instance: serotonin-dopamine antagonists, multi-acting receptor-targeted antipsychotics "MARTA", and dopamine partial antagonists [19]. Agents belonging to both of these categories differ in many properties, including efficacy, side-effects, cost and pharmacology, thus they do not form two distinct homogenous classes (even the agents of the same category do not show homogeneity), thus this generalized categorization (1st and 2nd) according to some clinicians, is improper, and can cause confusion and thus it might be best to be abandoned [20].

As a clinician, a psychiatrist considers many aspects in order to prescribe the medicine which will serve best to alleviate the symptoms and signs of psychosis and will cause the least harmful effects on the patient. These are, firstly, extrapyramidal symptoms "EPS" and, secondly, the antipsychotic efficacy of the agent to be used. We know that almost all antipsychotics have the propensity to cause EPS such as tardive dyskinesia as an unwanted effect. In contrast, the atypical agents can cause serious metabolic and/or hematological side effects.

Haloperidol

This butyrophenone derivative has the chemical formula

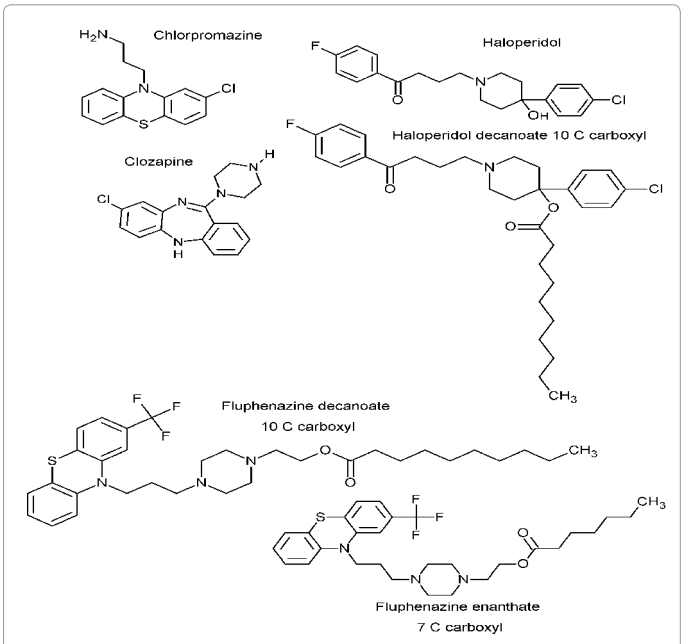

Figure 1: Chemical structures of the antipsychotic agents discussed.

"$C_{21}H_{23}ClFNO_2$" and has a molecular mass of "375.9 g/mol". It is a conventional (typical) antipsychotic agent. Haloperidol is metabolized in the hepatocytes of human liver via P450 3A4 to the neurotoxic pyridinium metabolites 4-(4-chlorophenyl)-1-(4-fluorophenyl)-4-oxobutylpyridinium (HPP+) and 4-(4-chlorophenyl)-1-(4-fluorophenyl)-4-hydroxybutylpyridinium (RHPP+) [21]. These two metabolites "HPP+ and RHPP+" are lipophilic compounds and have elimination half-lives of 67.3 hrs and 63.3 hrs, respectively [22]. HPP+ is a structural analog of MPP+ and its precursor MPTP. MPP+ is known as a Parkinson's producing neurotoxin; a fact that might explain why haloperidol exerts more EPS than any other antipsychotic agent [23]. The drug and the metabolites are excreted from the body by the renal system.

Clinical uses of haloperidol

Haloperidol is registered in the WHO's list of essential medicines. When it was newly discovered, it was considered to be an indispensable agent for treating psychiatric emergencies [24,25]. However, when we take a closer look at the literature between 2001-2005, we find that the newer (atypical) drugs have to a great extent replaced haloperidol [26,27]. A randomized, blind, placebo-controlled study, regarding the application of haloperidol in Alzheimer's patients with behavioral problems suggested that this neuroleptic antipsychotic actually worsened their conditions. The same study concluded that withdrawal of this agent for cognitive and functional measures was advantageous [28].

As is the case with other typical antipsychotics such as phenothiazines, haloperidol is by far more active against "positive" psychotic symptoms (delusions, hallucinations, etc.) than the "negative" symptoms (social withdrawal, etc.) [29]. In fact haloperidol is superior to many atypical antipsychotic agents in treating schizophrenia e.g. aripiprazole, quetiapine and ziprasidone for the acute treatment of psychosis in hospitalized patients with schizophrenia, schizoaffective disorder [30]. Indeed the results of a randomized clinical trial suggested that first-episode schizophrenia can be treated for at least 1 year of therapy with haloperidol. The same study did not conclude that 2nd generation agents have a higher level of efficacy than haloperidol [31]. Some important uses of haloperidol are shown in Table 1.

Route of administration, depot preparations

When orally administered, haloperidol has a bioavailability of about 50-60%. When administered by intramuscular injection as haloperidol decanoate, it is rapidly absorbed and has a high bioavailability. The oily decanoate formulation is designed only for intramuscular administration. The plasma concentrations of haloperidol decanoate reach a peak at about six days after the injection, falling then gradually, and the half-life is then approximately three weeks [32].

Intravenous injection causes a very rapid onset of action, within seconds. That is why this form of administration is considered for psychiatric emergencies where an antipsychotic agent is promptly required. When given by the intravenous route the bioavailability is 100%, and it has duration of action of almost 5 hours. If haloperidol is given as a slow intravenous infusion, the onset of action is slowed, and the duration of action is prolonged. The decanoate ester of haloperidol is a depot form of this agent, the IUPAC name of which is 4-(4-chlorophenyl)-1-1[4-(4-fluorophenyl)-4-oxobutyl]-4 piperidinyl decanoate. This lipid soluble preparation has a longer duration of action, and it is available for deep intramuscular use, injected at regular intervals of 2-4 weeks for patients that have not demonstrated compliance for oral use.

The therapeutic serum concentrations of haloperidol lie between "2-15 ng/ml", see Table 2 [33,34]. It is important to check the serum concentration from two points of view: firstly, for adjustment of the therapeutic dose (titration) and secondly, to check the patient's compliance in chronic cases. It is worthy of mention that also as in the case of phenothiazines, the concentration of haloperidol in brain tissue is about 20-fold higher compared to serum concentration. The drug is gradually eliminated from brain tissue [35], and this might explain the slow disappearance of side effects when the medication is

Psychoses of different etiology
Drug-induced psychoses: such as with LSD (lysergic acid diethylamide), psilocybin, amphetamines, ketamine, and phencyclidine. Psychoses of metabolic or febrile reasons. Bipolar depressive disorder: acute phases and in refractory phases combined with lithium or valproate. Agitation and hyperactivity: as in catatonic schizophrenia. Acute delirium: of different etiology. Borderline personality disorders: therapeutic trial.
Neurological disorders
Cerebral sclerosis: agitation and confusion.
Treatment of certain neurologic disorders: tic disorders, Tourette syndrome, and different types of chorea.
Uncontrollable behavioral disorders: in children and adolescents.
Other uses
Alcohol and opioid withdrawal: as an adjunctive treatment. Antiemetic: in post-operative and palliative care (radiotherapy, chemotherapy at oncology clinics).
Pain therapy: adjuvant to analgesics.
Data obtained from [133-143].

Table 1: Some important clinical uses of haloperidol.

Drug	Daily dose, mg	Elimination t/2 hours	Therapeutic serum concentration ng /ml	Toxic serum levels
***Chlorpromazine**	50-450	24	30-300	>750
Haloperidol	2-20	24	2.0-15.0	>18
Clozapine	150-600	12	100-700	>2000
*Chlorpromazine is included for comparative purposes. Data adapted from [33,34,37].				

Table 2: Therapeutic and toxic serum concentrations of antipsychotic agents.

stopped [35,36]. Adverse effects and contraindications of haloperidol are presented in Table 3.

A Brief Comparison to Phenothiazines

When comparing side effects exerted by haloperidol with those of phenothiazines, taking chlorpromazine as an example, one can mention the following: We note that haloperidol causes low sedation, and there is a reduced possibility of causing seizures compared to chlorpromazine. They both exhibit a low incidence of weight gain and provide moderate chances of prolactin elevation. Haloperidol has low anticholinergic side-effects compared to chlorpromazine. The major disadvantage of haloperidol over chlorpromazine is that the incidence to get EPS is very high [37,38] (Table 4). Another important difference is that the daily dose of haloperidol (2-20 mg) is much less than chlorpromazine (50-450 mg) (Table 4), thus the therapeutic serum concentration of haloperidol is by far much less than that of chlorpromazine. This fact indicates that haloperidol is more potent than chlorpromazine, although both have a linear titration relationship pattern.

Clozapine

This is an atypical antipsychotic agent, with the formula "$C_{18}H_{19}ClN_4$", having a molecular mass of 326.823 g/mol. This dibenzodiazepine derivative is used clinically in treatment of schizophrenia and bipolar disorders. Clozapine was the first atypical neuroleptic to be designed and produced. It was introduced in many western European countries in the early nineteen seventies. The drug was demonstrated to be effective in treating resistant cases of schizophrenia where there was no response to conventional antipsychotic agents [39].

Unfortunately, clozapine showed a devastating side effect, namely the occurrence of agranulocytosis which led to sudden death. This was the reason behind the withdrawal of this antipsychotic remedy from the drug markets in certain countries, such as USA, for a certain period. Therefore regular white blood cell counts, particularly neutrophils, are necessary when clozapine is prescribed for patients [40,41].

Serum concentrations of clozapine and its metabolite norclozapine may be monitored, though we have to bear in mind that these can show a significant degree of variation, firstly, because of sex they are higher in women than in men and secondly, concentrations increase with age [42]. Other advantages of monitoring the serum concentrations of clozapine and norclozapine are that the values are useful in assessment of compliance and cooperation of the patient (as in the case with haloperidol), metabolic status, prevention of toxicity, and titrating the optimal dosage [43]. In general, clozapine should be reserved for cases where other drug-lines of two different groups do not give the anticipated clinical effects [44].

The basic idea, or the reason behind designing this atypical agent (and the others), is to treat drug resistant cases of schizophrenia and especially in treatment of negative symptoms of schizophrenia such as apathy, avolition, poverty of speech, poor self-esteem and social withdrawal [34].

Metabolism of clozapine

The oral bioavailability of clozapine is only 60-70% after complete absorption; this is attributed to the first-pass metabolism of the drug. Peak serum concentration of the agent is reached after almost 2.5 hrs. The clearance half-life of clozapine is about 14 hrs; this varies depending on the daily dose administered. The drug is almost entirely catabolized by the cytochrome P450 system to hydrophilic active metabolites, the major of which is norclozapine (desmethyl-clozapine), which in turn is excreted in the urine and by the feces.

Dose dependent adverse effects**
EPS effects: manifested mainly as movement disorders and tardive dyskinesia later on. **Akathisia:** manifests itself as anxiety, dysphoria, and inability to remain motionless. **Anticholinergic side effects:** such as dry mouth, constipation, tremors. **Weight gain:** complications of obesity and metabolic syndrome. **Mood changes:** deep depression with suicidal risk during long-term treatment.
Non-dose dependent adverse effect
NMS: manifested as hyperthermia, muscle rigidity, autonomic instability, cognitive changes and elevated creatine phosphokinase. **Allergy:** skin rashes, photosensitivity, occur in less than 1% of patients. **Sudden death:** because of heart block (QT-prolongation seen in EKG).
Absolute contraindications of the agent
CVA: acute stroke, and comatose patients. **Intoxication:** alcohol or other CNS depressants. **Allergy:** against haloperidol or other butyrophenones or other drug ingredients of the preparation being used. **Preexisting cardiopathy:** tends towards causation of cardiac arrest
Data obtained from [81,144-149]. **long-term use or when given in high doses.
EPS: extrapyramidal symptoms. NMS: neuroleptic malignant syndrome.

Table 3: Adverse effects and contraindications of haloperidol.

Antipsychotic	Daily dose (mg)	Sedation	EPS	Anticholinergic	Orthostatic	Seizures	Prolactin elevation	Glucose tolerance	Weight gain
***Chlorpromazine**	50-450	High	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low
Haloperidol	2-20	Very low	Very high	Very low	Very low	Low	Moderate	Low	Low
Clozapine	150-600	High	Very Low	High	High	High	None	High	High
Nine parameters have been taken in consideration for comparison between (chlorpromazine versus haloperidol) and (haloperidol versus clozapine). Respectively these are: the daily dose; sedation; EPS (extrapyramidal effects); anticholinergic effects; orthostatic effects (hypotension); seizures; prolactin elevation; glucose tolerance and weight gain. * Chlorpromazine is included for comparative purposes. Data obtained from [33,34,38].									

Table 4: Comparison of side effects of chlorpromazine, haloperidol and clozapine.

Clinical uses of clozapine

As stated previously, clozapine is an atypical (non-conventional) antipsychotic drug, prescribed primarily to patients who are unresponsive or intolerant of conventional antipsychotics such as haloperidol [45]. It is used principally in treating treatment-resistant schizophrenia. Treatment- resistant schizophrenia means an untreatable psychosis when at least two antipsychotic agents fail to alleviate the symptoms and signs in a satisfactory manner [46]. As mentioned before, clozapine has also been shown to be more effective in reducing negative symptoms of schizophrenia than the older conventional (typical) antipsychotics. In other words had more pronounced effects in the group of patients who responded poorly to other forms of medication.

The relapse rate of psychosis with clozapine is lower, the patients' acceptability is better, yet sometimes without observing clear significant benefits in overall function [45]. Patients with schizophrenia often abuse substances because of misjudgment and lack of insight and impaired cognition compared to other patient groups, and also because of polypharmacy, which is the case when psychiatric health care is poor, as is the situation in many developing countries. The existence of evidence showing that clozapine may reduce the propensity of substance abuse in schizophrenic patients is a positive point for this antipsychotic [47]. Clozapine even has an advantage over olanzapine (another atypical antipsychotic) in that it is used for reducing the risk of suicide in high-risk patients [48].

Clozapine works well against both positive (e.g. delusions, hallucinations) and negative (e.g., emotional and social withdrawal) symptoms of schizophrenia [49]. This agent, however, does not cause dyscognitive effects that are often observed with other antipsychotics, besides it has the capacity to increase the capability of the patient to react to the environment he/she lives in. This means the patients who are on clozapine therapy are good candidates for social rehabilitation [50]. In the psychiatric literature one can find many studies indicating that clozapine can be used as an effective treatment for the psychosis associated with schizophrenia, and it is relatively unique in its lack of producing Parkinsonian-like symptoms, even at high doses. This is in part because clozapine binds relatively weakly to the D_2 dopamine receptor, which is in comparison to the majority of other antipsychotics [51]. This might explain the high daily therapeutic doses and therapeutic serum concentration of clozapine in comparison to haloperidol and chlorpromazine required [52] to exert therapeutic effects (Table 2). The drug is used orally. To our knowledge there exists no parenteral or depot preparations for this agent currently.

Adverse effects of clozapine

Major side effects of clozapine include:

Blood dyscrasias: Clozapine carries the risk of initiating the development of bone marrow suppression manifested as agranulocytosis, leucopenia and neutropenia. The risk is highest within about three months into treatment and it decreases substantially after a year to less than 0.01% [53]. Patients who have experienced agranulocytosis when previously treated with clozapine should not receive it again (another contraindication). To decrease the chances of clozapine-induced agranulocytosis, vitamin C (L-ascorbic acid) the universal (versatile) antioxidant, should be added to the regimen of drug treatment when clozapine is the drug of choice [54].

Cardiovascular: Myocarditis, orthostatic hypotension, syncope [52]. Myocarditis is a documented serious and sometimes lethal side-effect of clozapine; it usually develops within the first month of the commencement of treatment [55]. Monitoring side effect guidelines advise checking "C - reactive protein (CRP)" and troponin at baseline and weekly for the first 4 weeks after clozapine initiation and observing the patient for signs and symptoms of myocarditis [56]. These two proteins are inflammation markers; the first is non-cardio specific and the second is cardio specific. The results of a case-control study confirmed that the risk of clozapine-induced myocarditis is increased by quickly increasing the rate of titration dose, because of high age, and due to concomitant anticonvulsant sodium valproate therapy [57].

Central nervous system: In addition to inducing seizures, clozapine lowers seizure threshold. It causes headache, syncope, sleep disturbance, sedation [58], depression, delusions, hallucinations, and induces obsessive compulsive symptoms. Similar to other antipsychotics (though rarely) clozapine can cause neuroleptic malignant syndrome [59]. It is believed that slow titration of the therapeutic dose to obtain the optimal serum concentration may minimize the risk of orthostatic hypotension and other adverse cardiovascular side effects. One has to be aware of synergistic sedating interactions of clozapine with other drugs such as benzodiazepines and thus avoid their concomitant use.

Reproductive system: Disturbance of libido and ejaculation failure during orgasm has been reported when using clozapine [60].

Weight gain and diabetes: Clozapine-induced hyperglycemia and diabetic ketoacidosis [61,62] are facts documented by case reports. Actually these unwanted effects are the most debated issues among clinicians. These effects are probably due to the property that the drug can decrease insulin sensitivity [63]. Because of the above-mentioned, caution is necessary when prescribing clozapine for diabetes patients and/or those that have the risk factors of developing diabetes. All patients receiving clozapine should have their fasting blood-glucose monitored regularly. The other issue that falls under this category is obesity [64]. These two metabolic factors namely: impaired glucose metabolism and weight gain are actually constituents of metabolic syndrome. These metabolic disturbances consequently increase the risk of development of cardiovascular diseases. Results from clinical research conclude that the atypical antipsychotics (clozapine and olanzapine) disturb the integration of metabolic harmony by making the body utilize lipids rather than carbohydrates (glucose) to produce ATP (energy currency) that is necessary for vital biosynthetic reactions in the body [65].

Two more issues need to be mentioned here, firstly, there exist data suggesting that clozapine may be likely to cause adverse metabolic effects, more than some other atypical antipsychotics such as risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole and paliperidone [66], and secondly, clozapine increases the chances of developing reactive radical species by decreasing the body's selenium reservoir [67].

Withdrawal effects: Rebound cholinergic effects are anticipated with sudden withdrawal of clozapine. These can be manifested as dyskinesia and psychotic disturbance. Family members and psychiatric care-givers, and additionally the patients themselves, should be informed about the symptoms. When discontinuing clozapine, gradual dose reduction is recommended in order to reduce the intensity of withdrawal effects [47,68,69].

Retarded gastrointestinal motility: Fecal impaction, paralytic ileus, acute megacolon, ischemia and bowel necrosis could be life threatening complications and should not be neglected or under-recognized [47].

Hyper salivation: Drooling can be met in patients using clozapine. The drug is actually an antagonist for the majority of the muscarinic receptors (M_1, M_2, M_3 and M_5), while it is a potent agonist for the M_4 subgroup, found in the salivary glands [69,70].

Minor side effects of clozapine

These include urine incontinence [71,72], muscle stiffness, sedation, tremors, and orthostatic hypotension. The risks of EPS, such as tardive dyskinesia, are much less with clozapine than typical (conventional) antipsychotics; this is attributed to clozapine's anticholinergic effects. EPS usually subsides after a switch from a conventional remedy to clozapine [23,39].

Contraindications of clozapine

Absolute contraindications are mainly two: Myeloproliferative diseases (agranulocytosis), and uncontrolled epilepsy. Other relatively important contraindications for its use are liver damage and cardiovascular diseases.

Clozapine versus haloperidol: When closely examining the content of Table 4, one can note the following: clozapine actually causes high sedation, high anticholinergic side effects, has high propensity to cause seizures, has high liability to cause glucose intolerance and weight gain compared to haloperidol. Another issue is that the daily dose of clozapine (150-600 mg) is much higher than that of haloperidol (2-20 mg). The high daily dose of clozapine might explain its serious side effects. The advantages of clozapine over haloperidol, according to the nine parameters set out in Table 4, are that it causes no elevation in prolactin levels and results in a very low EPS.

As a matter of fact, despite the serious side effects of clozapine, it is the best drug we have available if two other conventional antipsychotics of different groups do not alleviate the symptoms of psychosis, including the negative symptoms [45,46]. It is also believed that the chance of relapse during clozapine therapy is less than with other antipsychotics [73]. The side effects and comparison between these two agents is clearly seen in Tables 3 and 4.

Discussion

In general, psychiatric disorders are among the most common illnesses of humans [74]. The most common are depression, anxiety and adjustment disorders, accounting for almost 10% of cases, while psychosis, which, as a matter of fact is rare accounts for 1-2% [75]. In specialist psychiatric services psychoses are among the most common disorders [76]. The treatment of psychoses actually is a dilemma for psychiatrists. The general reasons for this are: firstly, no one convenient drug can be used against all kinds of psychoses, secondly, because of known and unknown factors, many types of psychoses do resist conventional treatment and patients do not respond despite proper drug treatment for lengthy periods of time. This makes the outcome of the radical treatment poor. We can add two more extra factors for developing countries such as Libya: the first being the state of unreliability of statistics with respect to psychiatric disorders, and the second being the cultural factor in such a society that makes the sufferers of psychiatric ailments not seek professional help, neither in general medical centers nor in specialist clinics.

The problem with psychiatric disorders generally, and psychosis especially, is that there are no known preventive measures to avoid psychoses. This is because of the absence of reliable markers that can give a clue with respect to the later development of the disease [77]. Even the evidence for the early commencement of management is not clear [78]. On the other hand there is some evidence that early intervention may improve, as a short-term outcome, those with psychotic episodes [74]. Moreover, prevention of the disease in its prodromal phase is of uncertain benefit and therefore is not recommended [79]. Avoidance of psychedelic drugs such as cannabis, cocaine and other potent cerebral stimulants e.g., amphetamines, is another preventive measure. Psychological intervention may reduce the risk of development of the disorder [80]. Psychoses, personality disorders, endogenous depressive disorders, and affective bipolar disorder run in families. Unfortunately the genetic factor is the corner issue in the aspect of etiology. Environmental factors also contribute to a certain extent with respect to predisposition to many types of psychoses.

Accumulated clinical knowledge has emphasized that the contemporary aims regarding antipsychotic drug treatment should include the following: firstly, treatment and alleviation of the most florid psychotic subjective and behavioral disturbances, secondly, to resettle the patient back to society and restore a normal or a near-normal life pattern. The latter is achieved by alleviating/diminishing the so-called negative symptoms of psychosis such as amotivation, flattened affect and social withdrawal [44]. Broadly speaking, notable and common adverse effects of antipsychotic agents are: EPS symptoms and hyper prolactinemia which are notably seen using typical antipsychotics, and weight gain and its metabolic consequences mainly seen with atypical.

When we consider the review on haloperidol we can conclude that this agent is probably marginally effective in the treatment of schizophrenia, on the other hand the drug has a broad spectrum of adverse effects. As stated earlier, haloperidol should only be used if treatment with other agents is not possible [81].

In test subjects haloperidol has been shown to increase dopamine activity up to 98%, after two weeks on a "moderate to high" dose compared to that observed in chronic schizophrenics. This is attributed to the upregulation of D_2 receptors in patients using haloperidol, a fact that might explain the reason why these patients get severe dyskinesia [82].

A serious side effect of HPD, resultant of chronic use, is loss of astrocytes and oligodendrocytes [83] and statistically insignificant neuronal loss of about 5% [84]. The consequence of these necrotic processes is a change in brain volume [85,86]. Observations from an animal model study produced similar results. A volume reduction of brain cortex of 10-12% was confirmed in rats which were given haloperidol at doses equivalent to those used in the clinic [87]. Permanent brain damage, resultant of encephalitis, is another devastating side effect of almost all antipsychotic drugs since these cause antipsychotic malignant syndrome (NMS) [88].

Pregnancy and lactation are two physiological events that women encounter during their reproductive lives. As regards the implication of these two antipsychotic drugs on lactation it is evident that possible effects of use of antipsychotics by lactating mothers are mostly unknown.

Chlorpromazine results in drowsiness and lethargy in breast-fed infants. Haloperidol is also secreted in significant amounts into the milk and this can cause EPS in babies [89]. With respect to clozapine, data again confirm that this atypical antipsychotic agent is secreted into the milk of the lactating mother causing sedation, decreased suckling, restlessness, irritability, seizures, and cardiovascular instability in infants. Concerning the effects of HPD on the embryo, it does not represent a major teratogenic risk. This issue, however, represents an area of real controversy, because other studies have linked the use of

haloperidol during pregnancy with limb reduction defects [89]. In women exposed to haloperidol [90], a study recommends that a level II ultrasound examination, with emphasis on the limbs, should be considered within the first trimester of pregnancy.

Gynecologists actually recommend (if possible) the avoidance of use of antipsychotics (and in fact any form of medication) in the first trimester of pregnancy to ensure a sound organogenesis in embryos [91,92]. The accepted general rule among clinicians is that haloperidol and clozapine should only be given during pregnancy if the benefit to the mother clearly outweighs the potential fetal risk. Concerning clozapine, it should only be used as an ultimate means in patients that have not responded to other antipsychotic treatments, this is for two reasons: firstly, the serious side-effects of the drug, secondly, the costs of continually monitoring blood samples because of the possible development of agranulocytosis [93].

A positive consideration with respect to clozapine is that its use is associated with a lower relapse rate of those suffering from psychosis. As has been stated before, phenothiazines (PTZs) (conventional, typical antipsychotics) are not potent drugs, and the side effects they can cause are tremendous. The same applies to haloperidol, although it is not a phenothiazine derivative. The real problem with conventional agents is that they are not very efficient in treatment of the negative symptoms of schizophrenia. This issue was the motivation to discover and apply new, more potent remedies to combat psychosis, therefore a series of new atypical agents were manufactured and marketed for this purpose. The idea was to attain a sort of convincing radical treatment, or a reasonable alleviation of the symptoms of psychosis. Many new agents such as amisulpride, aripiprazole, risperidone, olanzapine and others are currently in use in many countries and many are still at the experimental stage.

To enhance the actions of psychotropic drugs (here antipsychotics) new results recommend the use of PUFAs (Poly Unsaturated Fatty Acids) as a supplement during treatment. These essential micronutrients, though alone cannot be used to treat psychoses as a sole remedy, there exists solid evidence proving their significance in treatment of psychiatric diseases and ADHD as supplementary measures [94]. The PUFAs include omega 3 and 6 fatty acids (obtained from fish, olives and other vegetables in the diet) that humans cannot synthesize *de novo*, and these ensure the integrity of neuronal membranes, provide optimal alignment of receptors and affect cellular metabolism (membrane pace-maker theory) [95] .

Pharmaceutical chemists and antipsychotic drug designers are currently attempting to design and then manufacture an agent to treat negative symptoms of psychoses. Actually it is the negative symptoms of psychosis that hinder these individuals to integrate in society and keeps them in institutions. The current global trend in psychiatric health policy, however, is to deinstitutionalize these individuals (whenever possible) as, for example, is the case in Scandinavia.

The conclusion one can draw from a careful examination of the studies done on antipsychotic agents is that currently there exists no versatile, perfect drug for treatment of all psychoses. Each drug in use has its own particular advantages and disadvantages. The current situation thus necessitates the development of a so-called "ideal" or "near-ideal" remedy for these patients.

Because the atypical antipsychotics exhibit a lower incidence of EPS and are effective against the negative symptoms of psychosis, they are preferred over haloperidol and other conventional drugs in some clinics, and are therefore used as first choice medicines. When we discuss the concept of an ideal (or near-ideal antipsychotic agent), we have first to answer the following question: can psychoses be classified as one type of illness? It is indeed true that psychoses share the major criteria of delusions, hallucinations and loss of insight. Schizophrenia is special regarding negative symptoms and seems to be that form of psychosis most strongly associated with cognitive decline. The other serious issue is does drug-receptor interaction theory explain the whole picture of exerting therapeutic function? There is solid evidence showing that antipsychotic agents intercalate in biomembranes and thereby influence important biological processes within the cells [94].

The agent to be developed should fulfill the following criteria

1. The ideal agent should be effective in the form of a monotherapy, not interact with other antipsychotic drugs or other drugs being used for treating coexisting diseases. The agent should be effective against positive and negative symptoms of psychosis and restore the cognitive function and cause no relapse of psychosis after completion of the course of treatment.

2. The desirable agent should not cause a profound EPS side effect (tardive dyskinesia) as is the case with typical antipsychotics, and to a lesser extent with most atypical ones.

3. The drug should not have the propensity to cause addiction, drug tolerance or exhibit withdrawal effects. An agent having an amphiphilic structure might solve this dilemma. This is because lipophilic drugs that cross the blood-brain barrier and cell membrane and up-regulate neuronal receptors are most likely to be liable to cause the above mentioned problems.

4. The agent should not cause unnecessary sedation and/or other unwanted side effects. In other words it should be very selective, be potent in small doses, have a rapid onset of action (very short lag-period) and not result in the production of harmful metabolites which could potentially prolong unnecessarily the duration of drug action.

5. It should be non-expensive in use for both society and patients, and monitoring of the serum concentration (if required), should be performable by a reliable, quick and cheap method.

6. The drug should be handy and administrable by different routes such as, oral, i.v., i.m. depot etc. such that the clinician can choose the most appropriate method for different patient groups. This being based on the patients' compliance. If the parenteral route would be mandatory, then this should either be atraumatic or cause as little trauma as at all possible.

7. The drug should not cause the unpredictable complication namely neuroleptic malignant syndrome (NMS). This, unfortunately, is an almost unavoidable complication of virtually all currently used antipsychotic agents (typical and atypical).

8. Weight gain and its metabolic consequences such as diabetes type II, hyperlipidemia, and disturbance of thyroid function are some of the known metabolic complications of antipsychotic agents which the ideal drug should not induce.

9. Bone marrow suppression, blood dyscrasias such as thrombocytopenia, agranulocytosis, and leucopenia are known complications of clozapine. The new agent should not cause these.

10. The ideal antipsychotic agent being searched for should not disturb the integrity of biomembranes, especially those of neurons and mitochondria so as to ensure the propagation and the continuity of electron transport in such a way that phosphorylative biosynthetic

reactions and ATP synthesis are not hampered with. Abnormal mitochondrial function is actually an important feature in the etiology of schizophrenia [96-98].

11. In cases where necessary, such as in cases of overdose or attempting suicidal intoxication, the drug should be easily removed from the body.

12. For female patients of reproductive age, the ideal agent should not exhibit teratogenic properties or be secreted into milk during lactation.

13. The agent in question should contribute to deinstitutionalization that is it should be available as a depot preparation.

14. Serum drug measurement (in case necessary) should be linearly related to the dose of the agent given for therapeutic purposes (titration), as is actually the case for chlorpromazine, haloperidol, and clozapine.

15. It should not contribute to the development and release of reactive oxygen species as is the case for clozapine.

Why to have a better agent?

The motivation for marketing the atypical (second-generation) antipsychotics was to provide greater efficacy and result in reduced side-effects compared with the older (typical) medications. This, however, turned out not to be the case [99,100]. Controversy was initiated when a review article concluded that there were no major differences between the uses of these two major categories of drugs [19]. Other studies concluded that atypical were only moderately more effective [101]. These claims were reviewed by other groups, where it was actually concluded that clozapine, amisulpride, olanzapine and risperidone were more effective than the typical remedies [19,102]. For instance, olanzapine in patients experiencing first-episode psychosis had a risk-benefit profile significantly superior to that of haloperidol, in other words 2nd generation antipsychotic agents (e.g., olanzapine) should be preferred when considering first episode psychosis, on the basis of being both safe and efficient [103]. It is worthy of mention that clozapine has proved to be more effective when compared to other second generation antipsychotics [19,104]. It is true that clozapine has been disfavored because of its grave side effects. The accuracy of many studies concerning the comparison between typical and atypical agents is actually in question because of statistical bias [105]. The preference of prescribing atypical over typical antipsychotics was indeed questioned by many research groups, some of these even questioned if there is any point behind making a distinction between the two major category classes [106-108]. On the contrary, other scientists ban the typicals because of the high risk of tardive dyskinesia and EPS symptoms. For this reason alone they recommend atypical ones in first-line treatment, without considering the propensity for developing adverse metabolic effects [109,110]. Many countries including the UK and those in Scandinavia, recommend that the choice should be based on individual evaluation, being dependent on the drug profiles and on the desire of the patient [111].

It is true that the new atypical preparations such as amisulpride, a selective dopamine antagonist, have different dose-dependent clinical uses e.g., in doses higher than 400 mg reduces the positive symptoms of schizophrenia while in lower doses it improves the negative symptoms of the disorder. This agent in low doses could be also used as an antidepressant, as an anxiolytic and has certain indications for treating dysthymia [112-114]. The drawbacks of amisulpride are, however, enormous, the most significant of which are:

Hyperprolactinemia: Because of D_2 receptor antagonism and its consequences.

Weight gain: More than haloperidol, lurasidone, ziprasidone and as much as aripiprazole and asenapine [115].

Anticholinergic effects: Urinary retention, tachycardia, agitation and confusion.

EPS side effects: Tremor, bradycardia, dystonia, acute and tardive dyskinesia [115].

Psychoneurologic effects: Headache, hyperactivity, somnolence and anxiety.

Rare side effects: These are dangerous and include, blood dyscrasias (leucopenia, neutropenia, agranulocytosis), and QT interval prolongation [115].

Aripiprazole: is a partial D_2 receptor agonist, unlike all other clinically used antipsychotics [116]. It is basically indicated for treating schizophrenia, bipolar disorder and major depression though as an adjunct, tic disorders and irritability associated with autism [117-121]. One can see that aripiprazole has miscellaneous clinical uses, on the other hand though it has a very wide range of side effects, and unfortunately almost all the side effects of both typical and atypical antipsychotics are accumulated in this agent [122-125]. This is attributed to the fact that this agent works on a huge number of receptors in the brain and elsewhere in the human body.

Olanzapine: It has versatile clinical uses as other atypicals; it is used in schizophrenia, acute manic episodes, and in maintenance of bipolar disorder. The principal side effect of this atypical agent is weight gain (greater propensity than other antipsychotics) which in some cases is associated with dyslipidemia and hyperglycemia. Again the spectrum of side effects of this agent is so wide that it is almost comparable to typical old antipsychotics [126-128].

Zotepine: This is indicated for acute and chronic schizophrenia, still in use in certain countries, while discontinued in other countries like Germany because of serious side-effects.

As we have seen, all currently available antipsychotics are associated with a long list of side effects, a reason that many people discontinue their drug therapy [129].

One can understand that these new agents are among the best we have, but still they are not the best we hope to have available in the future. Taking into account the facts cited in this review we thus propose the design of a hybrid structure aimed to provide a better antipsychotic with best possible efficacy on the one hand and least unwanted side effects on the other. We therefore took haloperidol from the first generation group and clozapine. What is the best drug currently available? This is a perplexing question, extremely difficult to answer. This is because even the modern atypical antipsychotics are heterogeneous both in their efficacy and side effect spectra, thus have to be evaluated individually [130]. When considering the advantages and disadvantages of haloperidol compared to those of clozapine, one would favor clozapine [131]. But we do have to admit that patients show therapeutic responses of huge variation following the use of both agents, and also to other antipsychotics, this being dependent on both known and unknown factors. This is simply attributed to the fact that we do not have a complete understanding of the real pathophysiology

of psychosis. The biological changes in the brain, both structurally and biochemically, clearly need to be more fully understood before one can discuss the issue of radical drug treatment of psychosis (psychoses). Some scientists even extract evidence from comparative studies where at least some schizophrenic individuals have in fact recovered from psychosis without using antipsychotics, moreover, they may in the long term function better than patients who do take antipsychotics [132]. These arguments remind us that we do not yet know all about the biochemistry of the brain cells and the pathophysiology of psychiatric diseases in general and psychosis in particular. It is a fact that atypical antipsychotic agents are superior to the older atypical agents; evidence shows a difference in their actions, mechanisms, therapeutic effects and side effects. The most recently investigated field in which both classes of drugs have opposing effects is neuron survival and neurogenesis [86].

Conclusion

The "hybrid structure" proposed in this review might give us a clue of how to prepare a better agent(s) that includes all the advantages of haloperidol and clozapine but is devoid of their life-threatening side effects. When constructed the agents should go through first stage study in psychosis-induced rats by applying the methods of bioassay, for example, to see if it causes the side effects we are aiming to avoid and the therapeutic function we are predicting to see. The next step would be to monitor bioavailability of the drug i.e. the fraction of an unchanged administered dose of the drug that reaches the systemic circulation. This would be followed by preclinical and then clinical studies in volunteers against placebo (as control individuals). One would need to be realistic and rational in this future trial because it is understood that the real pathogenesis of psychosis is unknown, and the dopamine theory of psychosis cannot explain all dimensions of the psychotic picture.

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