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Evidences of possible side effects of neuroleptic drugs: A systematic review

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ABSTRACT

The premise that chronic neuroleptic treatment may induce decline in some schizophrenic patients has received considerable attention. This effect, typically called super sensitivity psychosis, has been accredited to neuroleptic induced changes in mesolimbic or mesocortical dopaminergic receptors. Both typical and atypical antipsychotics generations of medication tend to block receptors in the brain´s dopamine pathways which offers a number of harmful and undesired (adverse) effects including lowered life expectancy, extrapyramidal effects on motor control including akathisia (an inability to sit still), trembling, and muscle weakness weight gain, decrease in brain volume, enlarged breasts e.g. gynecomastia in men and milk discharge in men and women (galactorrhea due to hyperprolactinaemia), lowered white blood cell count (agranulocytosis), involuntary repetitive body movements (tardive dyskinesia), diabetes, and sexual dysfunction. In evaluating the risk of neuroleptic medication, the occurrence of its common side effects and uneasiness connected with these side effects should be determined. However, research has not established that neuroleptics cause the projected effect, and considerations of mechanism have not been alienated from those of causation. The focus of research in this area should be the concern or repudiation of a causal relationship between chronic neuroleptic use and psychotic relapse, even though at hand article would eradicate to researchers to find out a compiled revision on probable side effects of neuroleptic drugs.

1. Introduction

1.1. History of antipsychotic development

The original antipsychotic drugs were happened upon largely by chance and then tested for their effectiveness. The first, chlorpromazine, was developed as a surgical anesthetic. It was first used on psychiatric patients because of its powerful calming effect; at the time it was regarded as a non-permanent pharmacological lobotomy[1]. Lobotomy at the time was used to treat many behavioral disorders, including psychosis, although its effect was to markedly reduce behavior and mental functioning of all types. However, chlorpromazine proved to reduce the effects of psychosis in a more effective and specific manner than lobotomy, even though it was known to be capable of causing severe sedation. The underlying neurochemistry involved has since been studied in detail, and subsequent antipsychotic drugs have been discovered by an approach that incorporates this sort of information. The discovery of chlorpromazine′s psychoactive effects in 1952 led to greatly reduced use of restraint, seclusion, and sedation in the management of agitated patients[1], and also led to further research that resulted in the development of antidepressants, anxiolytics, and the majority of other drugs now used in the management of psychiatric conditions. In 1952, Henri Laborit described chlorpromazine only as inducing indifference towards what was happening around them in nonpsychotic, nonmanic patients, and Jean Delay and Pierre Deniker described it as controlling manic or psychotic agitation. The former claimed to have discovered a treatment for agitation in anyone, and the latter team claimed to have discovered a treatment for psychotic illness[2].

Until the 1970s there was considerable debate within psychiatry on the most appropriate term to use to describe the new drugs[3]. In the late 1950s the most widely used

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term was neuroleptic, followed by major tranquilizer and then ataraxic[3]. The first recorded use of the term tranquilizer dates from the early nineteenth century[4]. In 1953 Frederik F. Yonkman, a chemist at the Swiss based Ciba pharmaceutical company, first used the term tranquilizer to differentiate reserpine from the older sedatives[5]. The word neuroleptic was derived from the Greek (neuron, originally meaning sinew but today referring to the nerves). Thus, the word means taking hold of one's nerves. This may refer to common side effects such as reduced activity in general, as well as lethargy and impaired motor control. Although these effects are unpleasant and in some cases harmful, they were at one time, along with akathisia, considered a reliable sign that the drug was working[1]. The term ataraxy was coined by the neurologist Howard Fabing and the classicist Alister Cameron to describe the observed effect of psychic indifference and detachment in patients treated with chlorpromazine[6]. This term derived from the Greek adjective Greek: (ataraktos) which means not disturbed, not excited, without confusion, steady, and calm[3]. In the use of the terms tranquilizer and ataractic, medical practitioners distinguished between the major tranquilizers or major ataractics, which referred to drugs used to treat psychoses, and the minor tranquilizers or minor ataractics, which referred to drugs used to treat neuroses[3]. While popular during the 1950s, these terms are infrequently used today. They are being abandoned in favor of antipsychotic, which refers to the drug's desired effects[3]. Today, minor tranquilizer can refer to anxiolytic and/or hypnotic drugs such as the benzodiazepines and nonbenzodiazepines which have some antipsychotic properties and are recommended for concurrent use with antipsychotics, and are useful for insomnia or drug-induced psychosis[7]. They are powerful (and potentially addictive) sedatives. Antipsychotics are broadly divided into two groups, the typical or first-generation antipsychotics and the atypical or second-generation antipsychotics. The typical antipsychotics are classified according to their chemical structure while the atypical antipsychotics are classified according to their pharmacological properties. These include serotonin-dopamine antagonists (see dopamine antagonist and serotonin antagonist), multi-acting receptor-targeted antipsychotics (MARTA, those targeting several systems), and dopamine partial agonists, which are often categorized as atypical[8].

2. Mechanism of the action of the neuroleptics

All antipsychotic drugs tend to block D_2 receptors in the dopamine pathways of the brain. This means that dopamine released in these pathways has less effect. Excess release of dopamine in the mesolimbic pathway has been linked to psychotic experiences. It is the blockade of dopamine receptors in this pathway that is thought to control psychotic experiences. It has also been proven less dopamine released in the prefrontal cortex in the brain, and excess dopamine released from all other pathways, has also been linked to psychotic expieriences, caused by abnormal dopaminergic function as a result of patients suffering from schizophrenia or bipolar disorder. Various nueroleptics such as haloperidol and chlorpromazine suppress dopamine chemicals throughout its pathways, in order for dopamine receptors to function normally. However, antipsychotics have numerous side effects such as extrapyramidal symptoms and brain shrinkage.

Typical antipsychotics are not particularly selective and also block dopamine receptors in the mesocortical pathway, tuberoinfundibular pathway, and the nigrostriatal pathway. Blocking D_2 receptors in these other pathways is thought to produce some of the unwanted side effects. They were commonly classified on a spectrum of low potency to high potency, where potency referred to the ability of the drug to bind to dopamine receptors, and not to the effectiveness of the drug. High-potency antipsychotics such as haloperidol, in general, have doses of a few milligrams and cause less sleepiness and calming effects than low-potency antipsychotics such as chlorpromazine and thioridazine, which have dosages of several hundred milligrams. The latter have a greater degree of anticholinergic and antihistaminergic activity, which can counteract dopamine-related side effects. Atypical antipsychotic drugs have a similar blocking effect on D_2 receptors. Some also block or partially block serotonin receptors (particularly $5HT_{2A,C}$ and $5HT_{1A}$ receptors): ranging from risperidone, which acts overwhelmingly on serotonin receptors, to amisulpride, which has no serotonergic activity. The additional effects on serotonin receptors may be why some of them can benefit the negative symptoms of schizophrenia[13].

3. Structural effects

Many studies now indicate that chronic treatment with antipsychotics affects the brain at a structural level, for example increasing the volume of the basal ganglia (especially the caudate nucleus), and reducing cortical grey matter volume in different brain areas. The effects may differ for typical versus atypical antipsychotics and may interact with different stages of disorders[14-15]. Death of neurons in the cerebral cortex, especially in women, has been linked to the use of both typical and atypical antipsychotics for individuals with Alzheimers[16].

Recent studies on macaque monkeys have found that administration of haloperidol or olanzapine for about two years led to a significant overall shrinkage in brain tissue[17], in both gray and white matter across several brain areas, with lower glial cell counts[18], due to a decrease in astrocytes and oligodendrocytes[19], and increased neuronal density. It has been said that these studies require serious attention and that such effects were not clearly tested for by pharmaceutical companies prior to obtaining approval for placing the drugs on the market[20].

4. Side effects of antipsychotics

Antipsychotics are associated with a range of side effects. It is well recognized that many people stop taking those (around two thirds even in controlled drug trials) due in part to adverse effects[21]. Extrapyramidal reactions include acute dystonias, akathisia, parkinsonism (rigidity and tremor), tardive dyskinesia, tachycardia, hypotension, impotence, lethargy, seizures, intense dreams or nightmares, and

hyperprolactinaemia[22]. Side effects from antipsychotics can be managed by a number of different drugs. For example, anticholinergics are often used to alleviate the motor side effects of antipsychotics[23]. Some of the side-effects will appear after the drug has been used only for a long time.

Some studies have found decreased life expectancy associated with the use of antipsychotics, and argued that more studies are needed[24]. In Feb. 2011, a minor loss of brain tissue was reported in schizophrenics treated with antipsychotics[25]. Brain volume was negatively correlated with both duration of illness and antipsychotic dosage. No association was found with severity of illness or abuse of other substances. An accompanying editorial said: The findings should not be construed as an indication for discontinuing the use of antipsychotic medications as a treatment for schizophrenia. But they do highlight the need to closely monitor the benefits and adverse effects of these medications in individual patients, to prescribe the minimal amount needed to achieve the therapeutic goal and to consider the addition of nonpharmacological approaches that may improve outcomes[26]. Continuous use of neuroleptics has been shown to decrease the total brain volume by 10% in macaque monkeys[27]. In healthy individuals without psychosis, doses of antipsychotics can produce the so-called negative symptoms (e.g. emotional and motivational difficulties) associated with schizophrenia[28]. From a subjective perspective, antipsychotics heavily influence one's perceptions of pleasurable sensations, causing a severe reduction in feelings of desire, motivation, pensive thought, and awe. This does not coincide with the apathy and lack of motivation experienced by the negative symptoms of schizophrenia. Detrimental effects on short term memory, which affect the way one figures and calculates (although this also may be purely subjective), may also be observed on high enough dosages. These are all the reasons why they are thought to affect creativity. Also, for some individuals with schizophrenia, too much stress may cause relapse.

Following are details concerning some of the side effects of antipsychotics:

(1) Antipsychotics, particularly atypicals, appear to cause changes in insulin levels by blocking the muscarinic M_3 receptor[29] (which is a key regulator of insulin secretion[30]) expressed on pancreatic beta cells and in regions of the brain that regulate glucose homeostasis. Altered insulin levels can lead to diabetes mellitus and fatal diabetic ketoacidosis[31-32].

(2) Antipsychotics may cause pancreatitis[33].

(3) Some atypical antipsychotics (especially olanzapine and clozapine) are associated with body weight gain partially due to occupancy of the histamine receptor[34] and changes to neurochemical signalling in regions of the brain that regulate appetite[35]. A metabolic side effect associated with weight gain is diabetes[36]. Evidence suggests that females are more sensitive to the metabolic side effects of atypical antipsychotic drugs than males[37].

(4) Clozapine also has a risk of inducing agranulocytosis, a potentially dangerous reduction in the number of white blood cells in the body. Because of this risk, patients prescribed clozapine may need to have regular blood checks to catch the condition early if it does occur, so the patient is in no danger [38].

(5) One of the more serious of these side effects is tardive dyskinesia, in which the sufferer may show repetitive, involuntary, purposeless movements (that are permanent and have no cure) often of the lips, face, legs, or torso. It is believed that there is a greater risk of developing tardive dyskinesia with the older, typical antipsychotic drugs, although the newer antipsychotics are now also known to cause this disorder.

(6) A potentially serious side effect of many antipsychotics is that they tend to lower an individual's seizure threshold. Chlorpromazine and clozapine, in particular, have a relatively high seizurogenic potential. Fluphenazine, haloperidol, pimozide and risperidone exhibit a relatively low risk. Caution should be exercised in individuals that have a history of seizurogenic conditions such as epilepsy, or brain damage.

(7) Neuroleptic malignant syndrome, in which the drugs appear to cause the temperature regulation centers to fail, resulting in a medical emergency, as the patient's temperature suddenly increases to dangerous levels.

(8) Dysphoria.

(9) Drug-induced Parkinsonism due to dopamine D_2 receptor blockade may mimic idiopathic Parkinsonism. The typical antipsychotics are more prone to cause this, compared to the atypical antipsychotics.

(10) Sexual dysfunction, which may rarely continue after withdrawal, similar to Post-SSRI sexual dysfunction.

(11) Dystonia, a neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures.

(12) Hyperprolactinaemia. The breasts may enlarge and discharge milk, in both men and women due to abnormally-high levels of prolactin in the blood. Prolactin secretion in the pituitary is normally suppressed by dopamine. Drugs that block the effects of dopamine at the pituitary or deplete dopamine stores in the brain may cause the pituitary to secrete prolactin.

(13) There is evidence that exposure may cause demyelinating disease in laboratory animals[39].

(14) Following controversy over possible increased mortality (death) related to antipsychotics in individuals with dementia, warnings have been added to packaging.

Some people suffer few apparent side effects from taking antipsychotic medication, whereas others may have serious adverse effects. Some side effects, such as subtle cognitive problems, may go unnoticed. There is a possibility that the risk of tardive dyskinesia can be reduced by combining the anti-psychotics with diphenhydramine or benzatropine, although this remains to be established. Central nervous system damage is also associated with irreversible tardive akathisia and/or tardive dysphrenia. The adverse effect profile of asenapine largely overlaps that of other atypical neuroleptics. However, asenapine can also cause oral hypoaesthesia and severe hypersensitivity reactions (angioedema, hypotension, skin reactions, etc). Tardive dyskinesia has also been reported with asenapine. Sublingual administration may be impractical during a manic episode. Other neuroleptics are available for patients who have difficulty swallowing, such as oral solutions and orodispersible tablets. In practice, clinical trials of asenapine were not designed to answer questions posed by healthcare professionals and patients. Asenapine is no more effective or convenient to use than other neuroleptics, while

it carries a risk of additional, sometimes severe, adverse effects. Patients with manic episodes should continue to receive lithium first, combined with a well documented neuroleptic such as haloperidol if they have severe psychotic symptoms. It can cause sedation and mild extrapyramidal side effects. Asenapine has a broad receptor affinity profile for most serotonergic, dopaminergic, and adrenergic receptors, with no appreciable affinity for muscarinic receptors. Asenapine may be a helpful treatment option for patients with schizophrenia when weight gain, dyslipidemia, and endocrine abnormalities are a concern[40].

A number of trials suggest that short term use of atypical antipsychotics may be useful in the treatment of delirium associated with critical illness. However, long term use of such agents for this indication has not been studied and may be associated with risks of adverse effects as well as unnecessary health care costs[41]. Rabbit syndrome is an antipsychotic induced rhythmic motion of the mouth and lips, resembling the chewing motion of a rabbit. The motion consists of vertical movement; the tongue is not involved[42]. Menstrual disorders are common among women with schizophrenia, particularly when they are being treated with antipsychotics. The occurrence of menstrual disorders is often attributed to the use of prolactin-elevating antipsychotics, although menstrual disorders also occur in patients not using antipsychotics[43]. Treatment of the positive psychotic symptoms of schizophrenia with standard antipsychotic drugs (APDs) is ineffective in a proportion of cases. For these treatment resistant patients the alternative is the APD clozapine which is superior to other agents but carries serious side effects[44]. Chronic amphetamine injection increased spontaneous neuronal activity in sensomotor cortex and decreased spike activity in caudate nucleus. The neuronal ability to perform the conditioned reactions was greater in the cortex and smaller in the nucleus caudatus[45]. Clozapine is often referred to as the gold standard for the treatment of schizophrenia and yet has also been described as the most underutilized treatment for schizophrenia supported by solid evidence-based medicine but other reasons for limited use of clozapine include the extra effort entailed in monitoring white blood cell counts to detect granulocytopenia or agranulocytosis and, possibly, minimal efforts to market it now that it is largely generic[46].

Dysphagia is a common symptom in the general population, and even more among psychiatric patients, but rarely seen as a sign of seriousness. It is a cause of death by suffocation, and more or less serious complications, and therefore should be diagnosed and treated. Among psychiatric patients, organic and iatrogenic aetiologies, as well as risk factors are identified, which worsen this symptom when associated[47]. Disruptive behaviour disorders include conduct disorder, oppositional defiant disorder and disruptive behaviour not otherwise specified. Attention deficit hyperactivity disorder (ADHD) is frequently associated with disruptive behaviour disorders. The difficulties associated with disruptive behaviour disorders are demonstrated through aggression and severe behavioural problems[48]. Agranulocytosis is a very serious side-effect of treatment with clozapine. For this reason, the Dutch guidelines state the specific values of leukocyte and neutrophil counts at which treatment with clozapine should be discontinued[49]. Neuropsychiatric symptoms such as agitation and delusions occur commonly in elderly patients with dementia and often cause significant distress. Adverse effects in patients with dementia include an increased risk of mortality and cerebrovascular events, as well as metabolic effects, extrapyramidal symptoms, falls, cognitive worsening, cardiac arrhythmia, and pneumonia[50]. Second-generation antipsychotics, clozapine and olanzapine have a high risk for causing weight gain and glucose dysregulation; iloperidone, paliperidone, quetiapine, and risperidone have a medium risk; and aripiprazole, asenapine, lurasidone, and ziprasidone have a low risk[51]. The myocardium have been get from 70 died patients sufferred from schizophrenia and treated by neuroleptic drugs. The cardiotoxic effect of neuroleptic drugs was characterized as adaptive, degenerative, and fibrous changes in the miocardium. In the extracellular matrix of the myocardium the processes of microcirculation and the collagenogenesis were damaged. As a result of the using neuroleptic drugs a compensatory hypertrophy of cardiomyocytes was transformed into their degeneration and atrophy that could be reason of a heart failure[52].

Man with schizoid personality disorder who suffered from a very focal and transparietal necrosis of the sigmoid after an overdose of atypical neuroleptics. This is a singular, rather unknown and potentially lethal side effect of these drugs[53]. In Japan, multiple antipsychotic drugs are administered at a high dose to schizophrenia patients, which is rare in other countries. Many of such patients suffer from side effects, among which extrapyramidal and autonomic side effects frequently occur. Many anticholinergic agents and cathartics are concomitantly used for schizophrenia patients, and their vital prognoses are likely to be poor[54]. Constipation is a common and potentially fatal side effect of clozapine treatment. Another important side effect of clozapine may also be significant weight gain. Clozapine cause agranulocytosis[55]. Classical antipsychotics, e.g. haloperidol, chlorpromazine, are potent at controlling the positive symptoms of schizophrenia but frequently elicit extrapyramidal motor side-effects. The introduction of atypical antipsychotics such as risperidone, olanzapine and clozapine has obviated this problem, but none of the current drugs seem to improve the cognitive deficits accompanying schizophrenia[56]. Conventional and atypical antipsychotic medications are approved by the FDA for treatment of schizophrenia and bipolar disorder. Over many decades, the widespread use of conventional antipsychotics produced various side effects[57]. Elevated cardiometabolic morbidity and mortality in patients with schizophrenia and bipolar disorder have been attributed to multiple sources, including antipsychotic treatment, which may adversely affect cardiometabolic risk factors[58].However, a 37 year old female presented with acute chlorpromazine and phenobarbital poisoning. Contrast enhanced abdominal CT on admission revealed a high density area at the gastric fundus and residual drugs were suspected[59]. The associated behavioural and psychological disorders associated with dementia frequently result in the prescription of antipsychotic drugs to assist in limiting disruptive or concerning unmet needs behaviour. Antipsychotic prescription rates in aged care facilities are estimated to be as high as 80% despite the well known adverse effects in this population[60] and patients with severe mental illness (SMI) treated with antipsychotic medication are at increased

risk of metabolic side-effects like weight gain, diabetes mellitus and dyslipidaemia[61]. Many antipsychotic drugs used to treat schizophrenia can cause amenorrhea in a significant proportion of women. The overall impact of this side effect has been little studied[62]. Transient prenatal vitamin D deficiency is considered a neurodevelopmental animal model in schizophrenia research. Vitamin D deficiency in female rats causes morphological, cellular and molecular changes in the brain and alters behaviour and nerve growth factors expression in their offspring[63].

Hyperprolactinaemia is a frequent but often neglected side effect of typical, but also of many atypical antipsychotics such as amisulpiride, risperidone or ziprasidone. Besides galactorrhoea, potential consequences are suppression of the hypothalamic-pituitary-gonadal axis with hypogonadism, sexual dysfunction, infertility and in women also irregularities of the menstrual cycle and amenorrhoea. Potential long term consequences are mainly osteopenia and osteoporosis with an enhanced risk of fractures[64]. Intrathecal morphine provides good analgesia after cesarean delivery but the side effects include nausea and vomiting. Low-dose droperidol (0.625 mg) combined with dexamethasone 4 mg is postulated to have an additive antiemetic effect with less side effects[65]. Sexual and reproductive function side effects of atypical antipsychotics are frequent, often underestimated and badly tolerated[66]. Morphine has been shown to be effective in providing analgesia after cesarean delivery, pruritus as a side-effect remains a common cause of dissatisfaction[67]. Hyperprolactinemia is a known side-effect of fluphenazine, a broad spectrum, long-acting phenothiazine known to be D_2 dopamine receptor antagonist[68]. Excessive bone mineral density (BMD) loss has been associated with schizophrenia, but its mechanisms and clinical implications are less clear[69]. Atypical antipsychotic drugs (AAPD) are widely used to treat severe psychiatric disorders, have well documented metabolic side effects such as disturbances in glucose metabolism, insulin resistance and weight gain[70]. The use of antipsychotic drugs has been associated with venous thromboembolism (VTE) in a number of reports. During the last decade the evidence has been strengthened with large epidemiological studies. Whether all antipsychotics increase the risk for VTE or the risk is confined to certain drugs is still unclear[71]. Central nervous system depressant drugs (CNS Ds) are known to impair cognitive functions[72] and in regards of above mentioned adverse effect of neuroleptic drugs and extreme level of possible side effect of certain drugs are revealed in given below (Table 1).

Table 1

Antipsychotic relative adverse effects (Ref: Partly reproduced from Maudsley 2001).

Drug	Sedation	EPS	Anti-cholinergic	Hypotension	Cardiac toxicity	Prolactin elevation	Weight gain
Clozapine	+++	-	+++	+++	+	-	+++
Risperidone	+	+	+	++	-	+++	++
Olanzapine	++	+/-	+	+	-	+	+++
Amisulpride	-	+	-	-	-	+++	+
Quetiapine	++	-	+	++	-	-	+

+ + + High incidence/severity; + Low; + + Moderate; - Very low.

5. Conclusions

The article has focused on various side effects of antipsychotics which are increasingly used off-label in geriaritic patients, as additional medication for various disorders and also prescribed to children and teenagers in specific cases. The article includes variety apparent side effects which have been noticed after administration of antipsychotic drugs, on continous administration in patients of various age groups, physiology, disease states and medical conditions. Some side effects, such as subtle cognitive problems, may go unnoticed like, Extrapyramidal reactions which includes acute dystonias, akathisia, parkinsonism (rigidity and tremor), tardive dyskinesia, tachycardia, hypotension, impotence, lethargy, seizures, intense dreams or nightmares, and hyperprolactinaemia. These side effects can be managed by a number of different drugs, like anticholinergics which alleviate the motor side effects of antipsychotics. There is a need to look after new therapeutic strategies for treatment of psychosis. Alteration in medication, multi drug combination therapy, administration of supplements etc can also help in improving these side effects. The presented review would be beneficial for the researchers working in the field of development of new drugs, with a well compiled data about the various side effects observed in patients after administration of antipscychotics to look forward for more effective strategies so as to eradicate this difficulty completely.

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