Neuro-Endocrinal Effects of Antipsychotics

An Essay

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By

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Mahmoud Abdelmegid Ibrahim

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List of Abbreviations

Abb.	Full term
5-HT	*5-hydroxytryptamine*
AAs	*Atypical' antipsychotics*
ACTH	*Adrenocorticotropic hormone*
ADH	*Antidiuretic hormone*
ALT	*Aminotransferases alanine aminotransferase*
AST	*Aspartateaminotransferase*
BMD	*Bone mineral density*
BPSD	*Psychological symptoms of dementia*
CAs	*Conventional antipsychotics*
CATIE	*Clinical Antipsychotic Trials of Intervention Effectiveness*
CHD	*Coronary heart disease*
CNS	*Central nervous system*
CRH	*Corticotropin-releasing hormone*
CVD	*Cardiovascular disease*
D	*Dopaminergic*
EEG	*Electroencephalographic*
EPS	*Extrapyramidal symptoms*
FDA	*Food and Drug Administration*
FGAs	*First-generation antipsychotics*
FSH	*Follicle-Stimulating Hormone*
GH	*Growth Hormone*
GHRH	*Growth hormone-releasing hormone*
GnRH	*Gonadotropin-releasing hormone*
H	*Histaminic*
HDL	*High-density lipoprotein*
HPRL	*Hyperprolactinaemia*
LDL	*Low-density lipoprotein*
LFTs	*Liver function tests*

List of Abbreviations (Cont...)

Abb.	Full term
LH	*Luteinizing Hormone*
Na	*Sodium*
NMS	*Neuroleptic malignant syndrome*
PET	*Positron emission tomography*
PNS	*Peripheral nervous system*
PP	*Polydipsia*
PRL	*Prolactin*
SGAs	*Second-generationantipsychotic*
SIADH	*Inappropriate secretion of antidiuretic hormone*
SPECT	*Single photon emission computed tomography*
SSRIs	*Selective serotonin reuptake inhibitors*
TD	*Tardive dyskinesia*
TRH	*Thyrotropin-releasing hormone*
TSH	*Thyroid Stimulating Hormone*
UR	*Urine retention*
VTE	*Venous thromboembolism*
α	*Adrenergic*

ABSTRACT

The aim of the work of the current study was to delineate the neuro-endocrinal effects of the antipsychotics and to highlight on the effect of using antipsychotics on the long run. In order to achieve that the researchers reviewed the available literatures and case studies done on the neuro-endocrinal effects of the antipsychotics.

Antipsychotics refer to drugs that are primarily used to treat symptoms of psychotic disorders such as schizophrenia and bipolar disorder. In 1950s, chlorpromazine (the first antipsychotic) enter the psychiatric practice, whereas, in late 1960s clozapine (the first second-generation antipsychotic) is introduced into clinical practice.

Keywords: *Luteinizing Hormone - Neuroleptic malignant syndrome - Positron emission tomography*

INTRODUCTION

Antipsychotics have now been used for over 50 years. They have benefited patients that would otherwise have been disabled by their symptoms and it has improved their quality of life. However, antipsychotics are no different from other drugs as they can cause minor but also serious adverse events leading to poor adherence, hospitalization and even death. Therefore, the medication's adverse effect profile is often an important deciding factor when choosing an antipsychotic. Sufficient data have been gathered over the past decade on the pharmacological profile and clinical adverse events to recognize that atypical antipsychotics (AAs) differ among themselves and they represent, as do conventional antipsychotics (CAs), a heterogeneous group of drugs ***(Landry et al., 2010).***

All antipsychotic drugs produce dopamine receptor blockade in the brain. Furthermore, there is a good correlation between *in vitro* antagonism of dopamine receptor sites and clinical antipsychotic potency for the standard antipsychotic drugs ***(Creese, 1985).*** Chlorpromazine was the first chemical compound recognized to possess specific antipsychotic activity. This compound is a phenothiazine derivative. Since the advent of chlorpromazine, a number of phenothiazines have been marketed as antipsychotics. Four additional distinct chemical structures have yielded a limited number of compounds that act

similar to chlorpromazine. Compounds within these five groups are considered to be standard antipsychotic drugs. Recently, newer drugs with a pharmacological profile different from chlorpromazine have been found to be effective in the treatment of schizophrenia. These agents are known as atypical antipsychotic drugs ***(Holland et al., 1991).***

Conventional antipsychotic agents differ in their ability to pass the blood–brain barrier. Because the pituitary gland lies outside this barrier, one would expect that drugs with poor brain penetrability and higher serum concentrations such as sulpiride ***(Mizuchiet et al., 1983)*** would have a greater effect on pituitary prolactin secretion. However, this has not been systematically investigated. The pharmacological basis of atypical antipsychotic action has been the target of intensive study, and various hypotheses have been put forward. These include a relative limbic selectivity of these agents, a separation of dose and response between pharmacological functions, interactions with neurotransmitter receptors other than dopamine receptors type 2, and the binding dynamics at the dopamine receptors type 2 ***(Kapur and Seeman, 2001).*** The serotonin receptors type 2 are involved in the stimulation of prolactin release, this usually occurs only at pharmacological levels of activation ***(Van de Kar et al., 1991).*** During antipsychotic treatment, prolactin concentrations can rise to ten times normal levels or above, and existing data indicate that 17^78% of female patients have amenorrhoea with or without

galactorrhoea. Survey data, however, suggest that clinicians underestimate the prevalence of these conditions. Long term consequences of antipsychotic-related hypo-oestrogenism require further research but are likely to include premature bone loss ***(Wieck and Haddad, 2003).***

Weight gain was originally noted with typical antipsychotics and is often a reason why patients wish to discontinue treatment. Some atypical antipsychotics are nevertheless associatedwith significantly more weight gain than typical agents ***(Malhe and Mitchell, 2003).*** This is believed to occur via increased appetite and food intake, which is mediated by central histaminergic H1-antagonism, with 5-HT2C antagonism having a synergistic effect. The increase in fat is accompanied by increased levels of the adipocyte regulatory hormone leptin. This weight gain is not clearly dose-dependent and substantial individual variation occurs ***(Lebovitz, 2003).*** Some clinicians recommend that patients with persistent dyslipidaemia should be considered for lipid-lowering agents or even switched to atypicals with less deleterious metabolic effects. Ziprasidone, aripiprazole and possibly risperidone are considered to have a lower risk for hyperlipidaemia ***(Meyer and Koro, 2004).***

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) investigated the continuation rate, effectiveness and Tolerability of four atypicals (olanzapine, ziprasidone, risperidone and quetiapine) with a typical

antipsychotic (perphenazine) in 1493 patients with schizophrenia ***(Stroup et al., 2007).*** Olanzapine had a significant advantage of over risperidone, quetiapine and perphenazine, but not ziprasidone, as measured by time to discontinuation dueto a lack of efficacy. Those patients on olanzapine, however, developed significantly more dyslipidaemia and weight gain than with the other drugs ***(Swartz et al., 2007).***

Acute intravenous administration of amisulpride to healthy volunteers elevates TSH levels in a dose-dependent manner, but less markedly than prolactin secretion ***(Wetzel et al., 1994);*** however, in most of the available studies, changes of TSH levels after dopamine agonists or antagonists were rather small or even demonstrable only in female or hypothyroid patients, respectively ***(Tuomisto and Ma¨nnisto¨, 1985).*** Antipsychotics differ in their potential to elicit seizures; chlorpromazine and clozapine as having the greatest risk ***(Haddad and Dursun, 2008),*** olanzapine, risperidone, quetiapine and ziprasidone generally have comparable risk, aripiprazole may confer lower risk ***(Hedges et al., 2003).***

Rationale of the work

Since the use of antipsychotics is going unsupervised in our community due to uncontrolled availability in the market, lack of psycho-education of the patients and their families beside their lack of regular follow ups in outpatient clinics, side

effects of such drugs are increasingly becoming the cause of associated neuro-endocrinal effects that can be the cause of morbidity, mortality, non –compliance of treatment plus the economic burden on the medical setting, which mandates reassessing such complication and reconsidering them in the treatment decisions.

Hypothesis

The primary objectives in the treatment of schizophrenia are to reduce the frequency and severity of psychotic exacerbations, ameliorate a broad range of symptoms, and improve functional capacity. Antipsychotic medications are the cornerstone of the pharmacologic treatment of schizophrenia. Despite the use of these agents for 60 years, however, schizophrenia continues to significantly limit the quality of life of a majority of affected individuals ***(Tandon, 2014).***

AIM OF THE WORK

1. To delineate the neuro-endocrinal effects of antipsychotics.
2. To highlight on the effect of using antipsychotics on the long run.
3. To categorize the neuro-endocrinal side effects of antipsychotics according to their dosages.