Comparing the side effect profile of the Atypical Antipsychotics.

***Adekola O. Alao, Kamna Malhotra and Mantosh J. Dewan**

Department of Psychiatry, SUNY Upstate Medical University,
750 East Adams Street, Syracuse. NY 13210.
E-mail: alao@upstate.edu

Summary

Typical antipsychotics exert their effect by blocking post-synaptic dopaminergic receptors; blockade of the mesolimbic and mesocortical pathways are therapeutic and help reduce positive psychotic symptoms but blockade of the nigro-striatal pathway[1] produces extrapyramidal side effects (EPSE). Post clozapine, the Food and Drug Administration (FDA) has approved the use of four newer atypical antipsychotics; risperidone, olanzapine, quetiapine and ziprasidone for the treatment of schizophrenia. Because of their dual serotonin and dopamine receptor blocking abilities, atypical antipsychotics have greater efficacy (especially for negative symptoms) and fewer EPSE when compared to the typical antipsychotics. Given the lack of studies directly comparing these agents, we used the Physician Desk Reference (PDR) to calculate the treatment emergent placebo adjusted side effects for these atypical antipsychotics. The results are then presented in an easy to read table. To the best of our knowledge, this is the first comparison study involving these four newer antipsychotic agents.

Key words. *Antipsychotics, Olanzapine, Quetiapine, Ziprasidone, Risperidone.*

Résumé

Cas des Antipsychotiquçs typiques exercent leur effets à travers l' obstructions des récepteurs dopaminergique postsynaptique, l'obstruction des sentiers mesolimbiques et mesocortiques sont thérapeutiques et ils aident à réduire des symptômes positifs de psychotiques mais l'obstruction des sentiers nigro-striatal[1] produit des réactions secondaires d'extrapyramidal (EPSE). Postclozapine, l'Administration de la nourriture et de la Drogue (FDA) avait ratifié l'utilisation de quatre antipsychotique, atypique, risperidone, olanzapine quetiapine et ziprasidone tout neufs pour le traitement de schizophrénie.

En conséquence de leur double récepteur obstruction fonctions, le sérotonine, et dopamine, l'antipsychotiques atypique ont une efficacité bien élevée (à l'égard de symptômes négatifs en particulier) et moins de EPSE par rapport à l'antipsychotiques typique. A cause du manque des études qui auraient provoquées une étude comparative et directe de ces agents, nous avons adopté la méthode de Physician Desk Reference (PDR) pour faire le calcul de traitement équilibré du développement d'effet secondaire placebo pour ces antipsychotiques atypique. Ainsi, les résultats sont présentés à travers un tableau facile à étudier. Autant que nous sachons, celle ci est la première étude comparative qui concerne ces quatre agents antipsychotiques tout neufs.

Introduction

Atypical antipsychotics were developed as a result of difficulties with the traditional antipsychotics, namely, the lack of improvement of negative symptoms and troublesome side effects such as extrapyramidal (EPSE) and tardive dyskinesia (TD). Typical antipsychotics exert their effect by blocking post-synaptic dopamine receptors, blockade of mesolimbic and mesocortical pathways are therapeutic and help reduce positive psychotic symptoms but the concomitant blockade of the nigro-striatal pathway leads to EPSE and TD. Atypical antipsychotics differ from typical antipsychotics in their "limbic specific" dopamine type 2 (D_2) receptor binding abilities and their high ratio of serotonin type 2 (5-HT_2) receptor binding to D_2 receptor binding capabilities[2]. The atypical antipsychotics have been found to be effective in the treatment of major depression with pyschosis, psychosis secondary to drugs use or general medical conditions, atypical psychosis, delirium, agitation, schizophrenia, schizoaffective disorder and agitation secondary to dementia. The first atypical, clozapine, is clearly more effective (and remains the gold standard for effectiveness) and has less EPSE but is plagued by the possibility of agranulocytosis and a number of other side effects.

After clozapine, the promise of greater efficacy (particularly for negative symptoms) and overall fewer side effects have made the four new atypical antipsychotics the first line in the treatment os schizophrenia. The first of the new atypicals, risperidone, was marketed in 1994 and is a benzisoxazole structurally different from haloperidol, clozapine and the phenothiazines. It has been approved for the treatment of schizophrenia[3]. Risperidone has strong affinity for D_2 and 5-HT_2 receptors, thus inhibiting the binding of dopamine and serotonin in specific areas of the brain[4]. It also binds to the alpha 1 adrenergic, histamine and alpha 2 adrenergic receptors[5]. It's affinity for serotonin 1c(5-HT_{1c}) is intermediate between clozapine and haloperidol and it has no affinity for 5-HT_3. Risperidone at doses of 4 mg/day or less is an atypical neuroleptic. However, it loses the atypical characterics at doses of 8 mg/day[6] and has an increased liability to cause EPSE.

Olanzapine is a thienobenzodiazepine, which has been approved for treatment of schizophrenia and is the only atypical antipsychotic approved for the treatment of bipolar disorder. It is similar to clozapine in structure and in its pharmacological properties. However, it has more favourable side effect profile when compared with typical antipsychotics[7]. Olanzapine has high affinity for 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, 5-HT_6, D_1, D_2, D_3, D_4, muscarinic M_1-M_3, alpha-adrenergic and histaminergic H_1 receptors[8]. It has been described to be more potent in inhibiting avoidance responses than in inducing catalepsy and causes selective depolarization of limbic A_{10} dopamine cells, suggesting low potential to develop EPSE[9].

Quetiapine is a dibenzodiazepine approved for the treatment of schizophrenia. It has affinity for multiple brain receptors with a higher affinity for central 5-HT_2 receptors than D_2 receptors[10]. Quetiapine has less potency when compared with clozapine at D_1, D_2, and 5-HT_2 receptor-binding sites in vitro. However, in vivo, this difference is less remarkable. Like clozapine , quetiapine shows limbic selectivity and has lower potential for causing EPSE. It restores pre-pulse inhibition in apomorphine treated rats with potency comparable to clozapine and produces induction patterns of neuronal F_{os} expression similar to that induced by clozapine but different from that induced by haloperidol[11].

Ziprasidone[12] is a novel antipsychotics with a high serotonin receptor affinity. Its pattern of receptor occupancy and pre-clinical attributes is predictive of a broad therapeutic efficacy. Clinical trials indicate that ziprasidone is effective against positive, negative and affective symptoms in schizophrenia and schizoaffective disorder. It is currently approved by the FDA for the treatment of schizophrenia and the only atypical approved for schizoaffective disorder.

There are no studies that directly compare all four of the newer atypicals on efficacy and side effects. The two studies comparing olanzapine and risperidone[13, 14] have conflicting results regarding

* *Correspondence*

the efficacy and tolerability of these two medications. Another study compared quetiapine and risperidone[15]. Following the method we used to compare antidepressants[16] and mood stabilizers[17], we assumed equivalent efficacy for the four atypicals and used data from the Physicians Desk Reference (PDR) to assess the tolerability of these agents.

Method

After reviewing standard textbooks of psychiatry, medline database and the PDR, we utilized the research data from the 2001 Physicians Desk Reference to construct a table comparing these atypical antipsychotics. The PDR is a yearly publication of the food and drug administration (FDA), which describes pharmacological products. The PDR describes the indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant warnings, hazards, contraindications, side-effects, and precautions. The FDA obtains these data regarding a new drug from companies manufacturing the drug. The data for olanzapine, risperidone, and quetiapine were obtained from the PDR. Data for ziprasidone was obtained from the ziprasidone package insert, which was approved by the FDA. We utilized the treatment emergent placebo adjusted incidence rate of side effects. This methodology is similar to that used in earlier studies on antidepressants[16] and the newer mood stabilizers[17] and has been replicated by Preskorn[18]. The following major categories of adverse effects were included in the calculation:

Gastrointestinal system: constipation, dyspepsia, nausea and vomiting. (Table 1).

Central Nervous System: somnolence, insomnia, EPSE (including tardive dyskinesia), (Table 2).

Other Systems: including weight gain, respiratory system (rhinitis, increased cough, laryngitis/pharyngitis, sinusitis, dyspnea) and cardiovascular system (postural hypotension, tachycardia and hypertension). (Table 3).

The PDR publishes treatment emergent side effects for each of these medications compared to placebo. We obtained the placebo adjusted incidence rates by calculating the difference in the incidence of treatment emergent side effects between the medication and the placebo. The total liability for each system was obtained by adding the incidence rates of each symptom rounded to the nearest 10th. Each figure obtained was converted into plus marks using a scale of 10% equaling one plus mark (1+). The potential of each of the four atypical antipsychotics was then presented in a table for easy understanding. The sum of all the plus marks was represented in a numerical estimate of the total side effect liability. Thus the higher the number, the higher the potential for side effects.

Table1 Placebo controlled adverse effect profile: Gastrointestinal system

Adverse Effect	Constipation	Dyspepsia	Nausea	Vomiting and diarrhea	Dry Mouth	Total
Olanzapine	6	--	--	--	3	9
Risperidone	4	1	3	1	--	9
Quetiapine	4	4	--	--	4	12
Ziprasidone	1	1	3	1	2	8

Table 2 Placebo controlled adverse effect profile - CNS

	Somnolence	Dizziness	EPSE*	Total
Olanzapine	11	7	6	24
Risperidone	2	3	1	6
Quetiapine	7	6	--	13
Ziprasidone	7	2	8	17

**EPSE=akathisia, dystonia, tremor and tardive dyskinesia.*

Table 3 Placebo controlled adverse effect profile: Weight gain, cardiovascular and respiratory systems

Adverse Effect	Cardiovascular System	Respiratory System	Weight Gain	Total
Olanzapine	4	8	5	17
Risperidone	--	12	--	12
Quetiapine	5	2	2	9
Ziprasidone	2	9	--	11

Results

As indicated in table 4, both risperidone and quetiapine have the most favourable adverse effect profile with a score of (3+).

Table 4 comparison table

	Olanzapine	Risperidone	Quetiapine	Ziprasidone
Gastrointestinal system	9 (1+)	9 (1+)	12 (1+)	8 (1+)
CNS/Psychiatry	24 (2+)	6 (1+)	13 (1+)	17 (2+)
Other Systems (including Cardiovascular, Respiratory Systems and Weight Gain	17 (2+)	12 (1+)	9 (1+)	11 (1+)
Total	5+	3+	3+	4+

Olanzapine has a score of (5+) while ziprasidone has a score of (4+). This finding is in contrast to an earlier study[14], which found a more favourable side effect profile in olanzapine treated patients, when compared with risperidone treated patients. Other studies[13] have shown comparable rates of side effects for these two medications. Both olanzapine and ziprasidone appear to have more CNS side effects (2+) when compared with risperidone (1+) and quetiapine (1+). This correlates with a clinical observation in which central nervous system depression was associated with 4 cases of olanzapine overdose[19]. All the four atypical antipsychotics have comparable gastrointestinal side effect liabilities with (1+) each. The short-term discontinuation rate for quetiapine and ziprasidone were the lowest at 4%. Olanzapine has a discontinuation rate of 7%, while risperidone has a discontinuation rate of 9%.

Discussion

This manuscript describes, with an easy to read table, the side effects of the atypical antipsychotics currently approved by the FDA for use in the United States. Drug tolerability indicates the likelihood of side effects caused by the drug, and whether or not these effects are distressing. Although, the main drawback of the typical antipsychotics is their tendency to cause EPSE, the tolerability of antipsychotics should go beyond that. For instance, in a study by Day et al.[20], adverse effects such as weight gain, menstrual difficulties, and lethargy were described as being more distressing than EPSE. Further, weight gain is significant because it increases the risk of high blood pressure, cardiovascular co-morbidity and may be socially unacceptable to the patient.

In presenting this data, we acknowledge several limitations of the study. The data from the PDR represents studies from different centers, conducted by different personnel and this may ultimately affect variables such as age, co-morbidity, and severity of illness. However, all studies used monotherapy with the respective antipsychotics medication, thus preventing potential contribution of the side effects from other medications. Secondly, some side effects may have been described with different terminology (e.g. both postural hypotension may refer to the same phenomenon). Thirdly, the total placebo adjusted treatment emergent rates of side effects for each category may be an exaggeration of the potential side effect liability. For example, while calculating the gastrointestinal side effect liability for risperidone, we totaled constipation (4%), dyspepsia (1%), nausea (3%), with vomiting (1%) for a total of (9%). However, less than 9%, of the subjects may suffer from these side effects as some may have all the four. This may exaggerate the potential gastrointestinal

side effect liability for risperidone. However, this confounding variable will affect all the four atypical antipsychotics making the table comparatively accurate. The study also did not take into account the potential for different dosages affecting the side effect liability. The threshold for the incidence of side effects reported also varied for these four antipsychotics. For risperidone, quetiapine, and ziprasidone the side effects reported occurred in 1% or more of the subjects. However, the side effects reported for olanzapine occurred in 2% or more subjects. Lastly, we could not include all the subcategories described in the PDR since they are not present across the board for all the four antipsychotic medications.

We also present the short-term discontinuation rates of the four atypical antipsychotics as an indirect method of assessing a number of factors such as severity (as opposed to frequency) of side effects, compliance, etc. Compliance may be affected by the affinity of medications. This describes the subjective feeling of benefiting from treatment with the medication, as opposed to feeling pressured to comply with taking the medication. Hence, non-compliance is an indirect way of assessing whether the adverse effects of the medications are subjectively worse than the perceived improvement by the patient. However, it has been suggested that patients may be more willing to accept the adverse effects of a medication if they know that the medications may be withdrawn eventually (as in many clinical trials). Thus, the data presented here should be interpreted in conjunction with the treatment emergent adverse effects. To illustrate this point, although risperidone had the least potential to produce side effects, it's use led to the most discontinuation (9%).

The PDR recommends that "the prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice. The figures however do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate." We present this data in the form of a table to serve as a guide in selecting an atypical antipsychotic and as a quick reference. Other factors such as previous response, efficacy, drug-drug interactions, physician and patient preference should be considered in the choice of an atypical antipsychotic.

Conclusion

We utilized the PDR to construct a table highlighting the potential of the newer atypical antipsychotics to cause side effects in the following categories (gastrointestinal, central nervous system, weight gain, respiratory and cardiovascular systems). This table is meant as a guide for the choice of the atypical antipsychotics. Individual differences in the adverse effect liability among these drugs should allow clinicians to choose the most appropriate drug for their patients. Ultimately, head to head studies involving all the newer antipsychotics (such as the one being currently sponsored by NIMH) will be required to solve the complex question of efficacy, effectiveness, and tolerability.

References

1. Gosselin O, Di Scala G, Ribeyere JM and Kahn JP.: New antipsychotic agents: new paths of research on the notion of atypical agents. Encephale 1996; 22 Spec No 6:3-6.

1. Worrel JA, Marken PA, Beckman SE and Ruehter VL.: Atypical antipsychotic agents: a critical review. Am J Health syst pharm 2000; 57:238-55.

3. Cardoni AA. Risperidone: review and assessment of its role in the treatment of schizophrenia. Ann Pharmacother 1995; 29:610-8.

4. Murray M. P450 enzymes: inhibition mechanisms, genetic regulation and effects of liver disease. Clinical Pharmacokinet 1992; 23:132-46.

5. Leysen JE, Janssen PM, Goomeren W, Wynants J, Pauwels PA and Jansen PA. In vitro and in vivo receptor binding and effects of monoamine tumor in rat brain regions of the novel antipsychotics risperidone and ocaperidone. Mol Pharmachol 1992; 41:494-508.

6. Arnt J and Skarsfeld T. Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence. Neuropsychopharmachology 1998; 18:63-101.

7. Fulton B and Goa KL: Olanzapine. A review of its pharmacological properties and therapeutic efficacy in the management of related psychosis. Drugs 1997;53:281-98.

8. Beasley CM Jr. Tollefson GD and Tran PV.: Efficacy of Olanzapine: an overview of pivotal clinical trials. J Clin Psychiatry 1997; 58 Suppl 10:7-12.

9. Stockton ME and Rasmussen K.: Electrophysiological effects of olanzapine, a novel atypical antipsychotic, on A9 and A10 dopamine neurons. Neuropsychopharmachology 1996; 14:97-105.

10. Saller CF and Salama AI. Seroquel: biochemical profile of a potential atypical antipsychotic. Psychopharmachology (berl) 1993; 112:285-92.

11. Robertson GS, Matsumura H and Fibiger HC.: Induction patterns of Fos - like immunoreactivity in the forebrain as predictors of atypical antipsychotic activity. J Pharmachol Exp Ther 1994; 271:1058-66.

12. Bagnall A, Lewis RA and Leitner ML.: Ziprasidone for schizophernia and severe Mental illness (Cochrane Review). Cochrane Database 2000; Syst Rev. 4: CD001945.

13. Ho BC, Miller D, Nopoulos P and Andreasen NC.: A comparitive effectiveness study of risperidone and olanzapine in the treatment of schizophrenia. J Clin Psychiatry 1999; 60:658-663.

14. Tran PV, Hamilton SH, Kuntz AJ, Potovin JH, Anderson SW, Beaseley C Jr and Tollefson GD.: Double-blind comparison of olanzapine verses risperidone in the treatment of Schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997; 17:407-418.

15. Mullen J, Reinstein M, Bari M, Crinsberg L and Sandler M.: Quetiaphine and risperidone in outpatients with psychotic disorder: result of the QUEST Trial Schizophrenia res 1999; 36-290.

16. Dewan MJ and Anand V.: Evaluating the tolerability of the newer antidepressants. J Nerv Ment Dis 1999; 187:96-101.

17. Alao AO and Dewan M. Evaluating the tolerability of the newer mood stabilizers. J Nerv Ment Dis 2001; 189:60-63.

18. O' malley GF, Seifert S, Heard K, Daly F and Dart R.: Olanzapine overdose mimicking opoid intoxication. Ann Emer Med 1999; 34:279-81.

19. Preskorn SH.: The relative adverse effect of non-ssri antidepressants: Relationship to in vitro pharmacology. Journal of psychiatric practice 2000; 6:218-223.

20. Day JC, Kinderman P and Bentall R.: A comparison of patients' and prescribers' beliefs about neuroleptic side effects: prevalence, distress and causation. Acta Psychiatric Scand 1998; 97:93-7.