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# A Review on Atypical Antipsychotics

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**ABSTRACT:**Atypical antipsychotics are the medication of decision for intense psychoses. They have less side effect of extrapyramidal indications when contrasted with the regular enemies of psychotics. The accompanying medications are gone under the average antipsychotics, such as, clozapine, olanzapine, quetiapine, ziprasidone, aripiprazole, asenapine, iloperidone, lurasidone, cariprazine, amisulpride.Second generation antipsychotics follows up on D2 dopamine receptors, as well as serotonin receptor opponent activity. 5H2A subtype of serotonin receptor is most usually include, tardive dyskinesia,Parkinsonism,steven-Johnson. The most atypical antipsychotics medications can cause unfavorable impact of weight gain, hyperlipidemia, ketoacidosis aside from ziprasidone and aripiprazole. They have some contraindications for the utilization of atypical maniacal medications syndrome, Agranulocytosis, seizures, and myocarditis are the FDA discovery cautioning depicting an extreme response to antipsychotics prompting death. Clozapine can cause serious neutropenia and so neutrophil count they screen.

**KEYWORDS:**Atypical antipsychotics, Extrapyramidal, Tardive dyskinesia, Agranulocytosis, Clozapine.

## I. INTRODUCTION

Atypical antipsychotic medications can be separated from conventional antipsychotics by their low or immaterial degrees of these undesirable results, by adequacy and all in all alleged expanded well-being. This last has been as of late addressed for the frequency of manifestations connected to metabolic syndrome. The various clinical and unfriendly impacts of various antipsychotics rely upon the blend of receptors inhabitance, yet the dopamine pathway is yet considered the essential normal objective for all antipsychotic drugs. Even more explicitly, no medication has yet been related to antipsychotic activity without a huge partiality for D2 receptors.[1,2] The administration of mental ailment during pregnancy is an inexorably significant, yet minimal got territory. Around the world, mental and conduct problems remain the main source of years lived with a handicap. For ladies, the pinnacle rate of numerous mental diseases, for example schizophrenia, happens during the reproductive years.[3,4]The advantages of remedial medication checking to enhance the viability of treatment and keep away from results or poisonousness were appeared. The wellbeing of patients, with the likelihood to utilize the least compelling portion, is an undoubted benefit of TDM. The productive and safe level is resolved at 60–80%. Considering the information on the signs for TDM and restorative fixation ranges, amisulpride, clozapine and olanzapine have the most significant level of suggestion to utilize TDM.[5]When contrasted and ordinary antipsychotics, they are less inclined to cause extrapyramidal manifestations and are better endured in the older. Simultaneously, reliable contrasts between atypical antipsychotics have been illustrated. Utilization of clozapine, for instance, is restricted by the danger of agranulocytosis, while this isn't a weakness of olanzapine, risperidone, quetiapine and even more as of late ziprasidone which are by and large broadly utilized with great outcomes in schizophrenia.[6]

### Mechanism Action Of Atypical Antipsychotics

The mechanism action of atypical antipsychotics can be classified into dopaminergic, serotonergic, and combined modulation effects.

### Dopaminergic modulation

Dopamine is a neuromodulator acting in the mind by methods for two essential gatherings of receptors. The D1 and D5 receptors have comparable structures and intra-cell flagging systems (expanded degrees of cyclic adenosine monophosphate [cAMP]) and are named 'D1-like

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receptors'. The D2, D3 and D4 receptors lessen cAMP levels and are named 'D2-like receptors.[7-9]

- Blockade of D2 receptors shared by all antipsychotics, ideal barricade is inside 65–75% of D2receptors, prompts adequacy with protected security (EPS and hyperprolactinemia).

- Blockade of D1 receptor is confined in PFC: remedial impact on negative and intellectual indications. D1 adjust movement of D2 (potentiation of effectiveness). D1 opposition alone no antipsychotic impact.
- Blockade of D4 diminishes catalepsy and incites dopamine discharge in the basal ganglia and PFC D4 enmity alone no antipsychotic impact.
- Blockade of D2/D3 - special enmity of inhibitory D2 auto receptors; expanded striatum (lower danger of EPS) and neocortical dopamine discharge (psychological and negative side effects).
- Blockade of D3 receptors in transient cortex, prompts stereo selectivity and adequacy on sure manifestations without acceptance of EPS.
- Rapid separation from D2 ("quick OFF") - more limited length of medication official to D2 is adequate for antipsychotic activity yet lacking to incite EPS and hyperprolactinemia (especially quetiapine and clozapine.
- Partial D2 agonism - aripiprazole, 30-40 % of inherent D2 receptor agonism regarding high D2 bar applies an antipsychotic impact with a generally safe of EPS and hyperprolactinaemia.[10-14]

**Serotonergic modulation**

From the verifiable perspective, interest in serotonergic adjustment for the treatment of schizophrenia emerged from the finding that 5-HT2A receptor agonists (for example lysergic corrosive diethylamide [LSD]) are solid hallucinogenic medications that can evoke crazy manifestations.[12,13]

- Blockade of 5-HT2A - 5-HT2A receptors incorporate cortical and subcortical sources of info. Enmity of 5-HT2A blocks the impact of NMDA adversaries and initiates striatal and neocortical dopamine discharge.
- 5-HT1A agonism - incites dopamine discharge into the striatum and neocortex (undifferentiated from 5-HT2A bar) and furthermore into limbic structures.
- Blockade of 5-HT2C - prompts neocortical dopamine discharge.
- Modulation of 5-HT2A, 5-HT1A and 5-HT2C alone no antipsychotic impact.[10,11,14-16]

**Combined modulation**

1. **Blockade of 5-HT2A and D2 receptors:** Higher proclivity for 5-HT2A receptors than for D2receptors prompts lower hazard for EPS (SDA and MARTA antipsychotics). 5 HT2A/D2 receptor opposition expands dopamine delivery to the PFC and striatum (improvement in negative and intellectual manifestations and lower EPS). Likewise substantial for incomplete dopamine receptor agonism with 5-HT2A enmity (aripiprazole) 5-HT1A receptor agonism and barricade of D2 receptors: expands dopamine delivery to the PFC, striatum, and limbic structures.
2. **Blockade of 5-HT2C receptors and barricade of D2 receptors:** Practically equivalent to 5-HT2A receptor bar or its help.
3. **Blockade of α-adrenoceptors and D2 receptors:** α1-adrenoceptor opposition diminishes movement of serotonin projections, and in blend with D2 receptor barricade would emulate/mimic 5-HT2A/D2 receptor enmity. Additionally, with α2-adrenoceptor opposition.
4. **Blockade of D2 receptors and connection with muscarinic receptors:** Lower danger of EPS and plausible supportive of psychological impact acetylcholinestimulation.[10,14,17]

**Induction of neuroplasticity**

Phosphorylation of receptors, potentiation of glutamate/glycine and induction of neuronal growth factors (NGF and BDNF): Reinforcement of NMDA receptor activity and development of new synapses or their remodeling.[16,18]

**THERAPEUTIC DRUG MONITORING**

Therapeutic drug monitoring of atypical antipsychotics affords the opportunity to reduce toxicity and increase adherence.[19]Nonetheless, the clinical benefit of utilizing plasma groupings of antipsychotics to screen patients with schizophrenia is a quarrelsome issue. Exorbitantly high focuses might be related with clinical crumbling of the patient because of antipsychotic harmfulness. The reasoning for utilizing remedial medication checking of atypical antipsychotics is as yet a matter of discussion, however there is developing proof that it can improve viability, particularly when patients don't react to helpful dosages or when they create unfriendly impacts.[20]The effective

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and safe level is resolved at 60–80% Therapeutic scopes of plasma convergences of the investigated drugs were resolved to be 200–320 ng/ml for amisulpride,[21] 150–210 ng/ml for aripiprazole,[22]more than 350–500 ng/ml for clozapine,50–500 ng/ml for quetiapine,[23]20–40 ng/ml for olanzapine,[24]20–60 ng/ml for risperidone and paliperidone,[25-27]50–100 ng/ml for sertindole,[28,29]and 50–130 ng/ml for ziprasidone.[30] The level of recommendation for the use of tdm in combination with the doses therapeutic concentrations of the discussed atypical antipsychotics isTable1.[31-36]

Amisulpride is an antipsychotic drug of the benzamide group. Its half-life is 12–20hr. The average therapeutic dose range is 300–800 mg/day. Amisulpride daily dose of 400–800 mg, plasma concentration of 200–500 ng/ml and safe levels (to avoid the extrapyramidal symptoms) within the range of 200–320ng/ml.[21]Aripiprazole has a place with the gathering of quinolinone subordinates. The half-existence of aripiprazole is distinctive relying upon the action of CYP2D6, inside the scope of 60–146hr.The protected and powerful plasma centralization of aripiprazole is proposed to be in the scope of 150-210ng/ml.[22]The suggested portion range is 15–30 mg/day.[22]Clozapine is a dibenzodiazepine subsidiary. Its half-life is 6–26hr, 12 by and large. The normal remedial portion is in the scope of 200–600 mg/day.[37,38]The many researchers try to determine the concentrations and therapeutic response thresholds for clozapine. The obtained results were different:200ng/ml,[39]420ng/ml,[40]By and large, 350–500 ng/ml is given as the base focus for helpful reaction, albeit the furthest reaches of the suggested fixations have not been established.[36] Olanzapine is gotten from thienobenzodiazepine and is an enemy of serotonin and dopamine. The normal remedial portion is 10–20 mg/day. The half-life of olanzapine is 37hr.[41] A restorative fixation scope of 20–40 ng/ml has been recommended, while focuses over 80 ng/ml can cause the event of antagonistic impacts.[24] Quetiapine is a benzodiazepine subsidiary. The half-life is around 7hr. The normal helpful portion in schizophrenia is in the scope of 200–600 mg/day.[42]The scope of focuses prescribed for grown-ups to bar unfavorable impacts is inside 70–170 ng/ml.[43]Different sources give a fixation range for the powerful treatment of schizophrenia at 50–500 ng/ml.[23] Paliperidone (9-hydroxyrisperidone) is a hydroxyl subsidiary of risperidone, its dynamic metabolite. Half-life is around 23–24 hrs. The normal oral helpful portion is 3–12 mg/day.[44]The restorative fixations scope of 20–60 ng/ml is proposed equivalent to for Risperidone.[27]Risperidone has a place with Benz isoxazole subsidiaries. After oral administration, the half-life is 3hr for risperidone, and 23–24hr for 9-hydroxyrisperidone. The normal helpful portion is in the scope of 2–4 mg/day. The remedial plasma centralization of risperidone will be inside the scope of 20–60 ng/ml.[25,26]Sertindole is an antipsychotic drug with the opposing activity on dopamine D2 receptors. Half-life is 55–90hr and the normal suggested remedial portion 12–20 mg/day.[45-47]Remedial plasma fixation range for sertindole is 50-100ng/ml.[28]Ziprasidone is a subordinate of piperazine. Half-life shifts relying upon the course of organization – after oral or intravenous organization it is 6–7hr, and after intramuscular organization 8–10hr. The normal suggested every day portion is in the scope of 120–160 mg.[29]The accomplished focuses affirmed the recently proposed helpful scope of 50–130 ng/ml and the relationship of portions with fixations.[30,48]

**Adverse Effects Of Atypical Antipsychotics**

Although the SGA drugs were at first promoted as having less unfriendly impacts inferable from their typicality, late proof has not upheld this case. Subsequently, the crisis care provider must be set up to remember them in the non-overdose setting. Most antipsychotics produce antagonistic impacts by 1 of 2 systems—portion related and eccentric. Peculiar unfavorable responses may happen with regards to routine restorative use and are identified with singular defenselessness, which is generally pharmacogenetic and just somewhat corresponded with portion. The antipsychotics, in contrast to numerous different classes of meds, have huge and even dangerous responses related with their utilization. Other normal unfavorable impacts are unsurprising, are portion related, and continue from their instruments of activity on different synapse frameworks as illustrated before, just as other biologic cycles. Weight gain is a more ongoing antagonistic impact that every now and again brings about treatment stopping an unpredictable issue for youngsters with mental illness. The following conditions are most regular unfriendly impacts of atypical antipsychotics drugs.[49,50]

**Weight Gain**

The basic antagonistic impact of antipsychotic drugs is weight gain which can be

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quickly increment and hard to control. It doesn't portion subordinate and considerably huge symptom of antipsychotic drugs and predominantly announced in grown-ups and youngsters. Olanzapine and Clozapine may cause more weight pick up when contrasted with other atypical antipsychotic medications, for example, >7% of the standard bodyweight in 40% or a greater number of patients.[51-54]It can likewise actuate cardiovascular and cerebrovascular dismalness and mortality diminished personal satisfaction and helpless medication consistence. Atypical Antipsychotic medications, for example, Quetiapine, Risperidone, Paliperidone, Sertindole, Zotepine have moderate danger of weight gain.[55]

**Anti-cholinergic effects**

Anti-cholinergic effects include constipation, urinary retention, dry mouth, blurred vision.[56] These effects are common with low potency first generation antipsychotics and clozapine.[57,58]

**Hyperprolactinemia**

It occurs mostly within a few weeks of beginning of treatment or increasing the dosage but can also arise after long-term stable use. It is a common with the use of any first-generation antipsychotic drugs as well as second generation antipsychotic drugs such as Risperidone and is dose dependent.[59]

**Cardiovascular**

Atypical antipsychotic may cause ECG changes such as prolonged QT interval and orthostatic hypotension,[51]Orthostatic hypotension occur with the low-potency second generation antipsychotic drugs such as Clozapine, Risperidone, Olanzapine, Quetiapine.[60]Atypical Antipsychotics most likely to cause ECG changes are low potency second generation antipsychotic drug such as Ziprasidone.[51,61]

**Sexual dysfunction**

It is very common and up to 49% of patients taking antipsychotic drugs report problems with sexual dysfunction, a distressing adverse effect that can lead to poor medication adherence.[62]Both FGAs and SGAs drugs can impair arousal and orgasm in men and women. Galactorrhea in women and men also gynecomastia in men is more common with second generation antipsychotics and with risperidone and can be dose related.[63]

**Sedation**

Sedation can occur with first generation antipsychotic drugs (such as Chlorpromazine, thioridazine and mesoridazine) and second-generation antipsychotic drugs (such as Clozapine, Olanzapine and Quetiapine), but it is seen more commonly and tends to be severe with low-potency first generation antipsychotic drugs than with second generation antipsychotic drugs.[64,65] Summary of the common adverse effects associated with the frequently prescribed atypical antipsychotic drugs is Table2.[64,65]

**Pharmacokinetics Of Atypical Antipyschotics**

**Clozapine**

Pharmacokinetic information from momentary investigations in patients accepting a fixed clozapine portion of showed wide interindividual range, with mean half-lives going from 9 to 17hr. An opportunity to arrive at the most extreme plasma fixation ($t_{max}$) was somewhere in the range of 1 and 4hr, plasma leeway was somewhere in the range of 9 and 53 L/hour, and the volume of appropriation was somewhere in the range of 2 and 7 L/kg.[66,67]After oral organization, the medication is quickly assimilated. Just 27–half of the portion arrives at the fundamental dissemination unaltered, due to ex-tensive first-pass digestion. Clozapine is 95% bound to plasma proteins, principally $\alpha_1$-acid glyco-protein.[68,69]Clozapine is significantly metabolized by the liver. Its significant metabolites incorporate nor clozapine, which may surpass groupings of the parent compound and has movement at the D2 and 5-HT2 receptors, and clozapine-Noxide, which can be metabolically diminished back to the parent compound.[70,71]Additional disposal items incorporate methylated, hydroxylated, and glucuronidase items.[72]Clozapine digestion gives off an impression of being interceded through numerous hepatic cytochrome P-450 isoenzymes including CYP1A2, CYP2D6, and CYP3A4.[70,73]

**Olanzapine**

Olanzapine is well absorbed, with a $t_{max}$of five to six hours.[66,67,70,71]Administration with food does not affect the rate and extent of absorption. The drug undergoes extensive first-pass metabolism. Oral bioavailability is approximately 60–80%.[73]Olanzapine is extensively distributed with a $V_d$of 10–20L/kg and is highly protein bound to both albumin and $\alpha_1$-acid glycoprotein.[73,74]Olanzapine exhibits a linear relationship between dosage and plasma concentration. The $t_{1/2}$ of olanzapine ranges from 20 to 70hr, which allows for single daily dosing. The drug reaches steady-state concentrations in five to seven days.[75]The main metabolite is the 10-N-glucuronide, and the cytochrome P450 system is

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involved in the formation of the other metabolites: the isoform 1A2 of cytochrome P450 is related to the formation of 4'-N-desmetylolanzapine, DMO, and the isoform CYP2D6 is related to the formation of 2- hydroxymethylolanzapine.[75]The major elimination pathways of olanzapine include direct N-glucuronidation with oxidative metabolism of 4′-Ndesmethyl olanzapine and 7-hydroxy olanzapine mediated through CYP1A2, 4′-N-oxide olanzapine through Flavin containing monooxygenase 3, and 2-hydroxymethyl olanzapine through CYP2D6.CYP2C19 may constitute a minor Pathway.[73]The elimination half-life of olanzapine is 21-54hr(immediate release)30days(extended release).[76]

**Risperidone**

Risperidone is rapidly absorbed after oral administration, with peak plasma concentrations being reached in about 1hr; it has good oral bioavailability at about 70–85%.[77]The mean half-life of Risperidone is 3hr in extensive metabolizers (the majorityof population), and 22 h in poor metabolizers; the mean half-life of the ''active moiety'' (risperidone and its main metabolite) is almost constant at about 22hr in bothgroups.[78] The drug is rapidly distributed with a $V_d$of 1–1.5 L/kg and is highly bound to both albumin and $\alpha_1$-acid glycoproteins.[79]Risperidone is principally metabolized by hydroxylation and N-dealkylation, with the major metabolite being 9-hydroxy-risperidone, which has similar pharmacologic activity and potency to the parent compound. This renally eliminated metabolite has a substantially longer $t_{1/2}$ (24hr) than the parent compound, and its formation is subject to genetic polymorphism of the debrisoquin type (CYP2D6).[70,73,79]The elimination half-life is 8-9 days (7-hydroxy-risperidone and glucuronides).[79]

**Ziprasidone**

The absolute bioavailability of an oral dose of ziprasidone 20mg under fed conditions is 60%. Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg.[80]Ziprasidone is highly metabolized in humans, with less than 5 % of the administrated dose being excreted in unchanged form. The initial metabolic pathway involves CYP3A4, which is responsible for two alternative oxidation pathways.[81]Elimination half-life of ziprasidone at the steady state has been reported to be 8–10hr.Age and sex do not have a clinically significant influence on the pharmacokinetics of ziprasidone.[82]

## II. DISCUSSION

Recommending atypical antipsychotic medications to individuals is trying because of the new proof of conceivable results; be that as it may, their judicious use may improve the personal satisfaction and practical status of old patients with neuropsychiatric illnesses. These medications are still frequently abused; the accessibility of data sets with longitudinal electronic wellbeing records of millions of individuals presents the chance to improve the information on the dangers and advantages of atypical antipsychotics in local area staying patients.[83,84]Atypical antipsychotics have been available since the 1990s, beginning with clozapine, they have been demonstrated to be viable in the treatment of negative indications of schizophrenia, for example, indifference and mental shock. In addition, they have exhibited lower dangers of EPS contrasted with traditional antipsychotics. Aripiprazole, quetiapine, and all the more as of late asenapine have been demonstrated to be successful in the treatment of the older with bipolar disorders.[85-88] Although the treatment of social issues in dementia with antipsychotics is off-name, antipsychotics are most likely the most ideal choice in the transient treatment (6–12 weeks) of extreme, tenacious, and safe aggression.[89]Serious unfavorable occasions are a significant contraindication to long term therapy.[90]Therapeutic drug monitoring is grounded for clozapine yet not a norm of care for the new antipsychotics. Except for olanzapine, the proof base that TDM advantageously affects treatment with new antipsychotics is still excessively powerless to use for the consideration of each patient. However long adequate proof is missing, TDM ought to be confined to extraordinary signs, for example, consistence control or results at remedially suggested dosages. Notwithstanding, the proof that TDM may have more extensive helpful impacts is developing. At a given portion, plasma centralizations of the new medications are profoundly factor among people. TDM can be utilized to discover if the patient grew amazingly low or high focuses. TDM may likewise be utilized as a legitimate marker of medication focuses on cerebrum, and significantly more significant, plasma fixations appear to be substantial proportions of dopamine receptor inhabitance. For olanzapine and risperidone, it appears to be likely that portion titration to a suggested helpful reach improves the reaction and limits results.[91,92]

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## III. CONCLUSION

In this review, atypical antipsychotics speak to another age of antipsychotics with a fundamentally lower occurrence of extrapyramidal results (EPS), just as almost no impact on prolactin elevation. The components activity on serotonin 5-HT2 or D4 receptors, or a quicker separation from the dopamine D2 receptor, may represent atypicality. Albeit the atypical antipsychotics have conquered EPS, opposite results, for example, weight acquire and impeded glucose resilience/lipid irregularities,sedation,cardiovascular impacts have gone to the front. TDM of antipsychotic drugs is a useful asset that permits fitting the treatment to the necessities of individual patients. It can help in checking adherence, in portion change, in limiting the danger of poisonousness and in expense adequacy in the treatment of mental issues. the significance of medication plasma level observing remaining parts with regards to recognizing "pseudo-pharmacoresistance" issues, for example, helpless consistence, high individual degrees of digestion, over the top water utilization by patients, extreme smoking, drug misuse, just as the presence of unpredictable side effects and possible drug interactions.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**ABBREVIATIONS**

**TDM:**Therapeutic drug monitoring; **EPS:**Extrapyramidal syndrome; **SDA:**Serotonin and dopamine antagonists; **MARTA:**Multiple–acting receptor targeted antipsychotics; **FGA:**First generation antipsychotics; **SGA:**Second generationantipsychotics;**BDNF**:Brain-derived neurotrophic factor; **NGF:**Nerve growth factor; **PFC:**Prefrontal cortex.

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**Tables and Tables legends**

**Table1: The level of recommendation for the use of TDM in combination with the doses and therapeutic concentrations of the discussed atypical antipsychotics.**

| DRUG | AVERAGEORAL THERAPEUTIC ANTIPSYCHOTIC DOSES [MG/DAY] | HALF-LIFE [h] | THERAPEUTIC PLASMA CONCENTRATION RANGE [NG/ML] | LEVEL OF RECOMMENDATION FOR TDM |
|---|---|---|---|---|
| Amisulpride | 300–800 | 12–20 | 200–320 | 1 |
| Aripiprazole | 15-30 | 60–146 | 150–210 | 2 |
| Clozapine | 200–600 | 6–26 | 350–500 | 1 |
| Olanzapine | 10-20 | 37 | 20–40 | 1 |
| Quetiapine | 200-600 | 7 | 50–500 | 2 |
| Paliperidone | 3–12 | 23–24 | 20–60 | 2 |

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| | | | | |
|---|---|---|---|---|
| Risperidone/ 9-OH-risperidone | 2-4 | 3/23-24 | 20–60 | 2 |
| Sertindole | 12-20 | 55–90 | 50–100 | 2 |
| Ziprasidone | 120-160 | 6–7 | 50–130 | 2 |

**Table 2: Summaryof the common adverse effects associated with the frequently prescribed atypical antipsychotic drugs.**

| DRUG | SEDATION | ANTI-CHOLINERGIC EFFECTS | POSTURAL HYPOTENSION | QTc PROLONGATION | WEIGHTGAIN | HYPER-GLYCAEMIA | HYPER-PROLACTENIMIA |
|---|---|---|---|---|---|---|---|
| Amisulpride | + | + + | + + | + + | + | + | + + + |
| Aripiprazole | + | + | + | Discrepant results | + | + | + |
| Clozapine | + + | + + + | + + + | + | + + + | + + + | + |
| Olanzapine | + + + | + + + | + | + | + + + | + + + | + + |
| Quetiapine | + + | + | + + + | + | + + | + + | + |
| Risperidone | + | + | + + + | + | + + | + | + + + |
| Sertindole | + | + | + + + | + + + | + + | + | + |

+ =Some effect.
+ + =Intermediate effect.
+ + + = Greatest effect