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RESEARCH ARTICLE

Polydipsia: Comparative action of two antipsychotics – Pimozide and ziprasidone

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ABSTRACT

Background: Primary polydipsia occurs without any central (vasopressin) deficit and/or peripheral (nephrogenic) organic impairment-associated with schizophrenia/obsessive compulsive disorder. In absence of associated symptoms/signs, it is idiopathic (might be preclinical/prodromic). Antipsychotics are tried with some claim but none is satisfactory. **Aims and Objective:** Unlike ziprasidone, pimozide misses D_1/muscarinic/adrenergic/histaminic actions - the experiment assessed its physiological manifestation and clinical potentials against polydipsia. **Materials and Methods:** Three batches of 21 Wistar male albino rats into two successive phases (viz. Normal and, after a washout period for 30 days, schedule-induced polydipsia) were divided into 3 groups (minimal, half maximal, and maximal dose). These 3 groups were divided into 3 subgroups of control, drug 1 and drug 2-each of 7 rats. Rat doses were "analogous" to permitted human doses. **Result:** Daily water intake lowering effect was evident only in polydipsic rats. Half-maximal dose of ziprasidone equated to maximal dose of pimozide. **Conclusion:** Ziprasidone (half maximal dose) can avoid the adverse drug reactions (ADRs) of pimozide (maximal dose) in humans polydipsia - though ADR manifestations may be wide-spread (more receptors involved).

KEY WORDS: Polydipsia; Schizophrenia; Pimozide; Risperidone; Body Weight

INTRODUCTION

Atypical Antidepressants as Two-edged Sword

Polydipsia/polyuria can be primary (also called psychogenic), central (due to decreased vasopressin), or nephrogenic (diabetes insipidus induced). Primary polydipsia/polyuria can be associated with schizophrenia or obsessive-compulsive disorder (OCD).[1]

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Although the treatment has never been satisfactory, propranolol <120 mg/day has been tried[2] and found effective mostly by inhibition of central renin-angiotensin system,[3] but antipsychotics are more relied.[4,5]

Making the matter more complex, polydipsia/polyuria can also be a symptomatic part of diabetes mellitus,[6] which in turn may be "coincidental with" or "due to" schizophrenia itself[7] or even iatrogenic, due to the antipsychotic treatment of schizophrenia.[8]

Annual unadjusted incidence rates of diabetes (new cases per 1000/year) were 7.5 for atypical antipsychotics, 11.3 for traditional antipsychotics, 7.8 for antidepressants, and 5.1 for antibiotics (though the report denies the difference between typical and atypical antipsychotics as statistically insignificant).[8]

Even before the introduction of antipsychotics, it was known that patients with schizophrenia are more likely to develop diabetes mellitus than the general population.[7]

More than 15% of drug-naive individuals with first-episode schizophrenia have impaired fasting glucose tolerance.[7] The accompanying Figure 1 summarizes the pathophysiological manifestations of schizophrenia and its modulation by atypical antipsychotic agents acting synergistically on some counts.[7]

Compared to non-antipsychotic psychotropic drugs, hazard ratio for antipsychotics for induction of diabetes mellitus is 3.03. Thus, antipsychotics are clearly responsible for new incidences of diabetes mellitus[9,10] and other closely related maladies such as weight gain and dyslipidemia.[11,12] Weight gain and dyslipidemia are also implicated indirectly in induction of diabetes among schizophrenics.[13]

Schizophrenia and antischizophrenic drugs both induce obesity.[13] Among atypical antipsychotics, aripiprazole and ziprasidone are safer on this count[13,14] which may be due to less affinity to histamine receptors.[15]

Autoimmune damages (e.g., By olanzapine and aripiprazole, through glutamic acid decarboxylase antibodies, insulin is damaged)[16] and inhibition of M_3 receptor-mediated insulin release (by clozapine/olanzapine)[17] are also involved in the etiopathology of diabetes mellitus.

Thus, unnecessary use of atypical antipsychotics (such as clozapine,[18] olanzapine,[4] quetiapine,[5] and even better-tolerated risperidone[4,19,18]) can increasingly induce diabetes mellitus[20] and thereby inducing polydipsia/polyuria than relieving the same.

Typical or classical antipsychotics can lead to many more diverse maladies[17] - for example, lithium is known to cause nephrogenic diabetes mellitus[17] while anticholinergic side effects of many antipsychotics induce dry mouth which may be another reason of polydipsia.[21]

Other risks of atypical antipsychotics are acute extrapyramidal symptoms (risperidone), hyperglycemia/dyslipidemia (clozapine/olanzapine), hyperprolactinemia (amisulpride/risperidone), QTc prolongation (ziprasidone/sertindole), and weight gain (clozapine/olanzapine).[22]

Polydipsia: Known Mechanisms and Managements

In general, psychiatric illness with high anxiety level and high positive and negative symptom scale grade are positively correlated to self-induced water intoxication.[23]

Schizophrenic polydipsia/polyuria correlates to D_2 polymorphism, for example, TaqIA variant (Ins-cys-A1 haplotype is quite resistant to such impairment).[24] Behind the widely accepted dopaminergic neuronal pathology traced down to molecular level, autoimmune oxidative damage[25,26] is also suggested.

It is notable here that haloperidol (D_2 antagonist-affinity more than most atypical antipsychotics) also induces reversal of polydipsia.[20] Moreover, atypical antipsychotics, in general, have lower affinity for D_2 receptors and higher affinity for $5HT_2$ receptors.[27] Explained by higher and lower Ki values, respectively, in the Table.[28]

Experimentally, panel pressing and temporal pattern of licking are more associated with D_1 receptors while stereotypy is more associated with D_2 receptor.[29] Thus,

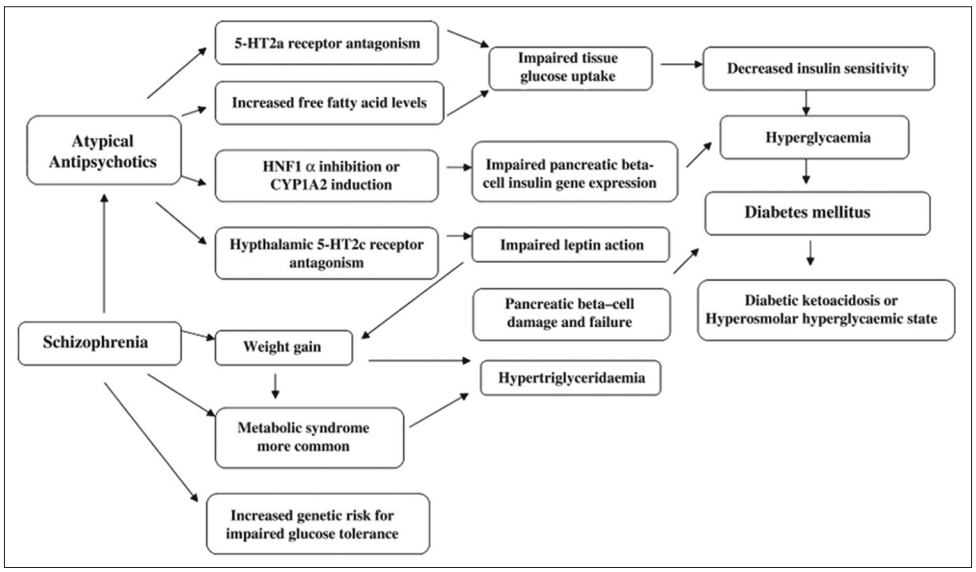

Figure 1: Proposed mechanism for antipsychotic-induced diabetes mellitus. CYP1A2: Cytochrome P450 1A2; HNF-1α: Hepatocyte nuclear factor 1α; 5-HT: 5-hydroxytryptamine

D_1 receptor modulation in itself is not directly involved in schizoid poplydipsia but behaviorally synergizes main D_2 action[30,31] and both might contribute in clozapine action against polydipsia.[29]

Besides, amphetamine-induced polydipsia is only partially prevented by D_2 selective domperidone, and this limitation can be explained by peripherally limited domperidone while polydipsia has mostly a central mechanism.[30] Different papers appreciating[29] and depreciating,[30] the role of D_1 receptors in polydipsia is explained by dose-dependant variation of amphetamine action.[31]

Amphetamine in low dose induces locomotor activity which is more distracting (hence reinstating the prior status) from polydipsia. However, stereotypy at high dose does not manifest the same way; rather it may induce OCD-like polydipsia.[31]

Although it is widely believed that amphetamine modulates dopaminergic action non-selectively, it is also notable that amphetamine sensitization could evolve under a D_1-independent mechanism since it was successfully developed in D_1 receptor knockout mice.[31]

Quinpirole ($D_{2/3}$ agonist[32]), after a transient suppression of instrumental behavior, increases water intake - the transient phase is abolished by amphetamine (induces hyperdipsia) but haloperidol (D_2 antagonist) inhibits this reversal effect of amphetamine.[30,31]

Thus, the increased water intake under influence of quinpirole has been related to more instrumental (operant) conditioning (characteristic of stereotypy called contrafreeloading[32-34]) than just an "extra urge" for water.[32]

In addition, central angiotensin-converting enzyme (ACE) is also involved in breakdown of bradykinin, and several neuropeptides such as enkephalin, dynorphin, neurotensin, and substance P[35] and genetic polymorphism thereof is implicated in schizophrenic polydipsia.[35,36]

Angiotensin receptor blocker irbesartan also reduces polydipsia[4] as ACE is involved in turnover of brain dopamine, and ACE polymorphism has been associated to polydipsia.[36] Notably, novelty seeking behavior is also correlated to ACE polymorphism.[37]

Interestingly, isradipine inhibits palatability induced polydipsia, but deprivation induced polydipsia is unaffected (showing the role of L-type Ca^{++} channels in dopaminergic pleasure performances).[38]

However, it is clearly established that lithium-induced polydipsia is mediated through dopamine and not renin/serotonin mechanism.[39] (through prepulse inhibition (PPI), dopaminergic as well as serotonergic (SERT) hypotheses of schizophrenia can be reached[35,40]).

PPI of the acoustic startle reflex is the reduction in the startle response when the startle-eliciting stimulus is immediately preceded by a weak stimulus. PPI, an operational measure of sensorimotor gating, is deficient in schizophrenia patients.[41]

Typical and atypical antipsychotics reverse PPI deficits produced by dopamine agonists such as amphetamine and apomorphine. The mechanism implicated has been blockade of D_2 receptors.[41]

In contrast, PPI disruption produced by noncompetitive non-competitive N-methyl-d-aspartate antagonists, such as phencyclidine or dizocilpine is antagonized by atypical but not typical antipsychotics and blockade of serotonin 5-HT_{2A} and/or α_1 noradrenergic, but not D_2 receptors, has been implicated in this effect.[41]

On the other hand, dopamine efflux at nucleus accumbens is selectively correlated to schedule-induced polydipsia (SIP) and not food-induced intermittent polydipsia (even nucleus accumbens is selectively involved in bouts of drinking, not the length, latency, amount, or onset).[42]

It is notable that if water is freely available to a rat that is food-deprived and subjected to an intermittent fixed timing schedule of food presentation, the rat will drink in large amounts concurrently with its operant execution in the reinforcement schedule. This behavior has been termed SIP.[43,44]

Adjunctive and displacement behaviors, esp SIP,[43] serve best as the animal model for novel drugs against OCD.[24] Normally, rats take 11 ml/100 g body weight/day,[45] but SIP rats may take >60 ml/day.[44]

Scopolamine potentiates the attenuating effect of SCH 23390 (selective D_1 antagonist) on SIP.[46] Diazepam reverses the attenuating effect (as gamma-aminobutyric acid ergic mechanism is also involved in polydipsia[47]) of SCH 23390 as well as cis-z-flupentixol (mixed $D_{1/2}$ antagonist) on SIP-raclopride (D_2 antagonist)-treated group is unaffected by the both.[48]

Concerning α_2 receptors, while clonidine increases percent of maximal weight gain, mianserin decreases it as well as polydipsia,[41] in which additional to action on dopaminergic dopamine transporter, added norepinephric transporter, and SERT transporter activity may be involved.[49]

Even naloxone has been found to induce PIP (psychosis, intermittent hyponatremia, and polydipsia) syndrome[50] as food/drink-related satiety/liking is related to opioid-dopamine interaction in nucleus accumbens.[13]

Oral V_2 receptor antagonist tolvaptan ameliorates hyponatremia in normal as well as schizophrenic populations.[51] However, hypernatremia itself is not inducing polydipsia (instead osmostat, i.e., Free water clearance versus osmolality graph is shifted to the left[52,53]).

Lesioned nucleus septus lateralis invokes polydipsia without increased appetite, and this is unaffected by dopamine or D_2 antagonist spiperone.[54] During psychotic exacerbations, unreasonable (despite low osmolality and hyponatremia) increase of antidiuretic hormone has also been elicited.[53]

MATERIALS AND METHODS

Drugs

As melperone, mesoridazine, and pimozide are the three drugs missing additional muscarinic, adrenergic, histaminic and even D_1 action,[55] the comparison of serotonin versus $D_{2/4}$ action is easier. In the present study, pimozide has been selected against ziprasidone.

After measuring food/water consumption and body weight, all the rat doses were given orally around 4.00 PM using prescribed gavage tube (needle curved, ball diameter 3 mm, length 3, gauge 16 G).[56]

Maximum allowed dose of pimozide (Larap-2 = 2 mg tablet used) is 0.2 mg/kg/day, i.e., 14 mg for 70 kg person. Although the ceiling dose is 10 mg/day, 4 mg is given on average,[55,57] and starting dose 1 mg/day in divided doses[58] (Table 1).

Rat body weight, compared to human, is (70 kg/200 mg =) 350 times less, but due to increased surface area, the dose ratio is 0.018, i.e., 56 times less only.[59] Notably, the $t_{1/2}$ of action pimozide is 29 h,[60] but elimination half-life of pimozide is 55 h.[61] For ziprasidon (Zipsydon 20 = 20 mg tablet used) minimal dose of 20 mg (for 70 kg man) - can be increased up to 160 mg/day.[62] Usual effective dose in humans is 80 mg.[63]

Study Design

Male Wistar rats weighing around 200 g (10 g) were housed at a light/dark cycle of 12 h each for a 1 week acclimation period with free access to food and water. Then, they were placed on a restricted diet which maintains 80% of their free-feeding body weight.[44]

During acclimation, food-water consumption and average body weight of individual and group were checked to confirm homogeneity of physiological parameters. Age (12 months) and sex (male) for all the rats were same. Total number of animals in each group was statistically decided using Mead's resource equation.[64]

The study is divided into 2 phases namely normal (phase I) and polydipsic (phase II)-each of 1 week, separated by a month of SIP procedure which also served as a washout period for the phase I drugs. Three such batches (of 21 rats each) with rat doses analogous to minimum, usual, and maximum human doses were run in parallel.

Thus, we got 18 groups of 7 rats each-9 groups before induction of SIP were as follows: NWN (normal rats on water), ND1N (normal rats on pimozide, minimal dose), ND2N (normal rats on ziprasidone, minimal dose), NWS (normal rats on water), ND1S (normal rats on pimozide, half maximal dose), ND2S (normal rats on ziprasidone, half maximal dose), NWX (normal rats on water), ND1X (normal rats on pimozide, maximal dose), and ND2X (normal rats on ziprasidone, maximal dose).

The same 63 rats were repeated after a month in another 9 groups, after induction of polydipsia, as follows: Polydipsic rats on water (PWN), polydipsic rats on pimozide, minimal dose (PD1N), polydipsic rats on ziprasidone, minimal dose (PD2N), polydipsic rats on water (PWS), polydipsic rats on pimozide, half maximal dose (PD1S), polydipsic rats on ziprasidone, half maximal dose (PD2S), polydipsic rats on water (PWX), polydipsic rats on pimozide, maximal dose (PD1X), polydipsic rats on ziprasidone, and maximal dose (PD2X).

RESULT

Findings of the studies are presented in Tables 2-6.

DISCUSSION

Analyzing the data outcome on SigmaPlot 13, the body weight of the rats before and after the induction of polydipsia was significantly different. As all the 63 rats were again used for the second phase of the study, a two-tailed paired *t*-test was run. The significance of this weight loss was not analyzed in the analogy of "primary" polydipsia in humans ("induction" of polydipsia might itself have played a role therein - hence a confounding factor).

When compared among themselves, the 3 batches (on minimal drug dose, half maximal dose, and maximal drug dose), before, or after induction of polydipsia, the difference of body weight was not significant. Expectedly, intake of water was significantly increased by induction of polydipsia.

On analysis of variance (ANOVA), the control rats (who were given plain water) in the three groups before (NWN, NWS, and NWX) or after (PWN, PWS, and PWX) induction of polydipsia, on the count of water intake, were not significantly different from each other.

Table 1: Calculation of drug dosing in rats

Drug	Tablet	Solution	Dose
Pimozide	Larap2 (2 mg)	50 ml (0.04 mg/ml)	1 mg (H); 0.018 mg (R) = 0.45 ml (N)
	Larap2 (2 mg)	10 ml (0.20 mg/ml)	7 mg (H); 0.126 mg (R) = 0.63 ml (S)
	Larap2 (2 mg)	04 ml (0.50 mg/ml)	14 mg (H); 0.252 mg (R) = 0.50 ml (X)
Ziprasidone	Zipsydon 20 (20 mg)	20 ml (1 mg/ml)	20 mg (H); 0.36 mg=0.36 ml (N)
	Zipsydon 20 (20 mg)	5 ml (4 mg/ml)	80 mg (H); 1.43 mg (R) = 0.36 ml (S)
	Zipsydon 20 (20 mg)	2 ml (10 mg/ml)	160 mg (H); 2.86 mg=0.29 ml (X)

(H): Human dose, 70 kg body weight; (R): Rat dose, 200 g body weight, (N): Minimal dose, (S): Half maximal dose, (X): Maximal dose

Table 2: Group-wise body weight before and after induction of polydipsia

Normal rats groups			Polydipsic rats groups		
On minimal dose	**On half-max dose**	**On maximal dose**	**On minimal dose**	**On half-max dose**	**On maximal dose**
198	190	206	200	195	198
192	194	190	189	193	187
210	198	205	181	193	199
203	206	203	191	184	182
207	207	191	189	198	193
207	192	190	196	191	194
199	205	210	185	198	191
204	199	206	200	193	182
208	209	206	195	184	189
201	197	208	181	195	198
200	191	200	184	186	183
210	198	198	180	189	200
200	202	191	186	192	191
198	200	203	187	198	196
201	193	196	190	185	189
199	201	195	199	193	193
209	192	192	195	181	199
206	195	200	199	198	183
201	194	191	195	198	195
196	192	205	193	183	190
194	206	198	182	181	186
(AV) 202.0476	(AV) 198.1429	(AV) 199.2381	(AV) 190.3333	(AV) 190.8571	(AV) 191.3333
(SD) 5.219925	(SD) 5.901574	(SD) 6.647592	(SD) 6.688298	(SD) 6.00238	(SD) 5.927338

AV: Average=arithmetic a mean; SD: Standard deviation

The difference in 9 normal rat groups at minimal (NWN, ND1N, and ND2N), half maximal (NWS, ND1S, and ND2S), or maximal (NWX, ND1X, and ND2X) doses was insignificant. Thus, the effect of the two drugs was not significant at any clinical dose in normal non-polydipsic rats.

On ANOVA, even at the minimal dose of the two drugs, the difference in 3 polydipsic rat groups (PWN, PD1N, and PD2N) was significant ($P < 0.0001$). Comparing control versus pimozide (PWN vs. PD1N) and control versus ziprasidone (PWN vs. PD2N) at minimal dose in polydipsic rats, a two-tailed unpaired T-test was run, and the difference was again significant.

Comparing ziprasidone and pimozide at minimal dose in polydipsic rats (PD1N vs. PD2N)), a two-tailed unpaired T-test was run, and the difference was again significant. Thus, ziprasidone fared better than pimozide even at the minimal dose.

On ANOVA, at half maximal dose of the two drugs, the difference in 3 polydipsic rat groups (PWS, PD1S, and PD2S) was still significant. Comparing control versus pimozide (PWS, PD1S) or control versus ziprasidone (PWS, PD2S) at half maximal dose in polydipsic rats, a two-tailed unpaired *t*-test was run, and the difference was significant.

Table 3: Body weight in various groups before the induction of polydipsia

NWN	ND1N	ND2N	NWS	ND1S	ND2S	NWX	ND1X	ND2X
198	204	201	190	199	193	206	206	196
192	208	199	194	209	201	190	206	195
210	201	209	198	197	192	205	208	192
203	200	206	206	191	195	203	200	200
207	210	201	207	198	194	191	198	191
207	200	196	192	202	192	190	191	205
199	198	194	205	200	206	210	203	198
(AV) 202.2857	(AV) 203.000	(AV) 200.8571	(AV) 198.8571	(AV) 199.4286	(AV) 196.1429	(AV) 199.2857	(AV) 201.7143	(AV) 196.7143
(SD) 6.317022	(SD) 4.50925	(SD) 5.273474	(SD) 7.12808	(SD) 5.442338	(SD) 5.336309	(SD) 8.635475	(SD) 5.908025	(SD) 4.820591

AV: Average = arithmetic a mean; SD: Standard deviation

Table 4: Body weight in various groups after induction of polydipsia

PWN	PD1N	PD2N	PWS	PD1S	PD2S	PWX	PD1X	PD2X
200	200	190	195	193	185	198	182	189
189	195	199	193	184	193	187	189	193
181	181	195	193	195	181	199	198	199
191	184	199	184	186	198	182	183	183
189	180	195	198	189	198	193	200	195
196	186	193	191	192	183	194	191	190
185	187	182	198	198	181	191	196	186
(AV) 190.1429	(Av) 187.5714	(AV) 193.2857	(AV) 193.1429	(AV) 191.0000	(AV) 188.4286	(AV) 192.0000	(AV) 191.2857	(AV) 190.7143
(SD) 6.388233	(SD) 7.367884	(SD) 5.908025	(SD) 4.810702	(SD) 4.966555	(SD) 7.699722	(SD) 6.00000	(SD) 7.111359	(SD) 5.437962

AV: Average=arithmetic a mean; SD: Standard deviation

Table 5: Average water intake of rats

Normal rats (Phase I)			Polydipsic rats (Phase II)		
Groups	**Average water intake (ml/24 h)**	**SD**	**Groups**	**Average water intake (ml/24 h)**	**SD**
NWN	30.71429	3.638419	PWN	64.14286	2.035401
ND1N	27.42857	3.047247	PD1N	55.00000	3.05505
ND2N	29.42857	2.992053	PD2N	50.28571	2.811541
NWS	30.14286	3.023716	PWS	64.14286	2.478479
ND1S	28.28571	2.497618	PD1S	51.14286	3.976119
ND2S	26.00000	3.785939	PD2S	45.71429	3.59232
NWX	29.28571	4.498677	PWX	63.42857	2.760262
ND1X	27.28571	4.231402	PD1X	43.85714	3.387653
ND2X	27.14286	3.532165	PD2X	41.14286	2.968084

Comparing ziprasidone and pimozide at half maximal dose in polydipsic rats (PD1S and PD2S), a two-tailed unpaired *t*-test was run, and the difference was significant. Thus, ziprasidone fared better than pimozide even at the half maximal dose too.

On ANOVA, at maximal dose of the two drugs, the difference in 3 polydipsic rat groups (PWX, PD1X, and PD2X) was still significant ($P \leq 0.0001$). At maximal dose, in polydipsic rats, comparing control and pimozide (PWX, PD1X) or control and ziprasidone (PWX, PD2X), the difference was again significant.

However, comparing ziprasidone and pimozide at maximal dose in polydipsic rats (PD1X, PD2X), the difference was unexpectedly insignificant. Thus, at maximal dose, the difference of effect of the two drugs is obscured.

At the same time, the effect of half maximal dose of ziprasidone and maximal dose of pimozide (PD1X, PD2S), there was no significant difference. Thus, rationally, half maximal dose of ziprasidone should be safer than the maximal dose of pimozide-though this fact was not clinically established in the current study.

Table 6: Statistical analysis of the data outcome

Comparators	Tests	Outcomes
Phase I versus Phase II (body weight)	two tailed paired *t*-test	*P*<0.0001; CI: 6.77-11.17
Phase I and II; (N) versus (S) versus (X) (body weight)	ANOVA	(*P*=0.098462) (I) (*P*=0.869641) (II)
Phase I versus Phase II (mean daily water intake)	two-tailed paired *t*-test	*P*<0.0001; CI (−27.00) - (−22.59)
Phase I, II; (N) versus (S) versus (X) (water intake)	ANOVA	(*P*=0.781460) (I) (*P*=0.820526) (II)
NWN versus ND1N versus ND2N	ANOVA	(*P*=0.189028) (I)
NWS versus ND1S versus ND2S	ANOVA	(*P*=0.072869) (I)
NWX versus ND1X versus ND2X	ANOVA	(*P*=0.559425) (I)
PWN versus PD1N versus PD2N	ANOVA	(*P*<0.0001) (II)
PWN versus PD1N	two-tailed unpaired *t*-test	*P*<0.0001; CI: 6.12-12.17
PWN versus PD2N	two-tailed unpaired *t*-test	*P*<0.0001; CI: 11.00-16.72
PD1N versus PD2N	two-tailed unpaired *t*-test	*P*<0.0001; CI: 1.30-8.13
PWS versus PD1S versus PD2S	ANOVA	(*P*<0.0001) (II)
PWS versus PD1S	two-tailed unpaired *t*-test	*P*<0.0001; CI: 9.14-16.86
PWS versus PD2S	two-tailed unpaired *t*-test	*P*<0.0001; CI: 14.83-22.02
PD1S versus PD2S	Two-tailed unpaired *t*-test	*P*<0.0001; CI: 1.02-9.84
PWX versus PD1X versus PD2X	ANOVA	(*P*<0.0001) (II)
PWX versus PD1X	two-tailed unpaired *t*-test	*P*<0.0001; CI: 15.97-23.17
PWX versus PD2X	Two-tailed unpaired *t*-test	*P*<0.0001; CI: 18.95-25.62
PD1X versus PD2X	Two-tailed unpaired *t*-test	*P*<0.1368 ; CI: (−0.99)-6.42
PD1X versus PD2S	Two-tailed unpaired *t*-test	*P*<0.3393; CI: (−5.92)-2.21

CI: Confidence interval at 95%; (N): Minimal dose, (S): Half maximal dose, (X): Maximal dose; (I): Phase I, (II): Phase II, ANOVA: Analysis of variance

CONCLUSION

Although no drug was significantly affecting the normal rats in terms of mean daily water intake, on polydipsic rats, ziprasidone faired better than pimozide, except when the both drugs were given in the maximal dose. The half-maximal dose of ziprasidone equated to maximal dose of pimozide. Thus, ziprasidone (half maximal dose) can avoid the adverse drug reactions of pimozide (maximal dose) in humans, but manifestation may be wider (more receptors involved). Weight loss, if similar in clinical studies on this line, can be an additional benefit-esp when antipsychotics are known to be responsible for new incidences of allied polydipsic maladies.[9-12]

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