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COMPARATIVE STUDY BETWEEN THE PHARMACODYNAMICS OF BENZODIAZEPINES AND THE AZAPIRONE CLASS OF ANXIOLYTICS BETWEEN TERTIARY HEALTH CARE CENTERS

Obstetrics & Gynaecology

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ABSTRACT

OBJECTIVE: Benzodiazepines are used for treating anxiety related disorders due to the limited knowledge of its pathophysiology. Elevated levels of serotonin are known to be associated with elevated mood. The aim of this study was to highlight the mood elevating property of azapirones in the plight of its already existing pharmacodynamic decrease of serotonin in comparison with benzodiazepines.

METHODS: A prospective observational case control study over two academic medical center's psychiatry department was performed from 1st August 2020 to 31st September 2020. Mood and anxiety symptom questionnaire (MASQ) was utilized to evaluate mood elevation in the subjects. Statistical analysis was done using MS – Excel 2021 updated edition.

RESULTS: 83.8% of the participants treated with azapirone showed mood elevation with adequate life satisfaction significantly [$t(28) = -14.30$, $p < 0.01$], compared to just 44.61% in the control group. Subjects treated with azapirones showed a better state of mental health. Gender adjusted chi-square analysis showed similar results in both male and females [$\chi^2(1, N = 37) = 5.11$, $p = 0.02$; $\chi^2(1, N = 59) = 8.11$, $p < 0.01$].

CONCLUSION: Patients belonging to the azapirone class of anxiolytic had a better post drug exposure and unbiased selection than compared to the group consuming benzodiazepines.

KEYWORDS

INTRODUCTION:

One of the greatest challenges for the recognition of the mechanism and the cure for anxiety is the overwhelming heterogeneity of the disorder. Anxiety is defined as feeling subjectively unpleasant of an irrational fear of futuristic events. It has been known to be associated with various attributes of numerous psychological disorders. Further, some of the most devastating symptoms such as somatic manifestations viz. presyncope and tremor are present in segments of the healthy general population. The 'Tripartite Model' explains the co morbidity between anxious and depressive symptoms and disorders. Studies in youth have revealed co morbidity rates of anxiety and depression as high as 70%. The most common association with generalized anxiety disorder and its numerous types are of depression, as explained and significantly proven by the 'Tripartite model'. Although past examinations of developmental trajectories as premorbid antecedents have focused on GABA neurotransmitter as the biological cause; altered properties of 5-HT and connectivity have been gaining more attention in the pathophysiology of anxiety disorders. Our inability to define sharp boundaries in the clinical presentation of the illness has hampered research efforts to identify treatments. There has been zero development of clearly demarcating any neuroanatomical abnormality that specifically distinguishes anxiety and depression from someone who is healthy. Innumerable number of drugs have been approved for the treatment, but there has been no growth to formulate and categorize that which patient should receive which medication. There are various studies showing the use of various classes of drugs for the treatment of anxiety and depression, but a few have shown some paradoxical controversy.

The two major classes of drugs used as anxiolytics are benzodiazepines and azapirones. After years of drug use and various randomized controlled trials, one controversy was surely faced but never addressed, that of the pharmacodynamics of the Azapirone class of anxiolytic.

The first drug to represent the class was buspirone. These medications worked differently on the manifestation of anxiety disorder and defined various other pathophysiologies for the same. The way it is better and different in action as compared to benzodiazepines is that it does not produce sedation. The conventional biological cause of anxiety is unhampered, that is, no GABAergic neurotransmission. Unlike benzodiazepines, there has been no reported case of physical dependence which prevents the patient from overdosing it.

The unusual story of azapirones creates a controversy in relation to its pharmacodynamics and clinical effect of the drug. The mechanism of the anxiolytic action is not clearly known yet, but there is a strong relation with 5-HT_{1A} receptor and is our primary focus. There is an inherent presence of 5-HT receptors in our body, and amusingly 5-HT_{1A} receptor is present on both the end of the synapses; viz. presynaptic and postsynaptic. Presynaptic receptors are otherwise called "auto receptors", where its action is used to bring about negative feedback. The drug acts as a partial agonist on the presynaptic auto receptor, thus reducing the activity of dorsal raphe serotonergic neurons. It also is a partial agonist for the postsynaptic 5-HT_{1A} receptor and again reduces its activity. Overall, the amount of 5-HT in the body falls and thus there is an endogenous depletion of the hormone created artificially by azapirones.

Along with many substances, viz. adrenaline, dopamine, oxytocin, etc.; 5-HT is one of the proven and known neurotransmitter to cause and maintain wellbeing in an individual. The quality of mood elevation is one of its major actions. And therefore, making the use of 5-HT stimulating, rather 5-HT_{1A} receptor agonistic drugs in depressed patients is considered adequate intervention. This statement holds true for selective serotonin reuptake inhibitors (SSRIs) which inhibit presynaptic axonal terminal and stimulate postsynaptic receptors for an extended period, as a result increasing 5-HT activity. The main aim of this study is to highlight the role of azapirone class of anxiolytics in decreasing 5-HT activity yet providing anti-depressant action.

METHODS:

Study design and participants

In this prospective observational case control study, we collected data from two academic medical center's psychiatry department affiliated with a government hospital in Mumbai, Maharashtra, India. The participants of the prospective case-control study provided verbal informed consent. This study was approved by the Institutional Review Board of both the institutions and conducted and reported in accordance with the STROBE guidelines.

Patients with generalized anxiety disorders (GAD) with symptoms of more than 6 months were included in this study (N=96) with age ranging between 20-40 years with randomization in gender selection. This cohort was selected from 1st August 2020 to 31st September 2020 and then divided into two groups based on their current treatment for GAD, i.e., patients with prescription alprazolam as control group (benzodiazepine [BZD] group) and the other with patients consuming buspirone (azapirone [AZP] group) considered as the study's primary case group. Kappa values for mood (0.89) and anxiety diagnoses (0.80) were high.

Measures

Mood and anxiety symptom questionnaire (MASQ)

These cohorts were then evaluated with the help of mood and anxiety symptoms questionnaire (MASQ). MASQ is a 77-item self-report questionnaire that assesses depressive, anxious, and mixed symptomatology was used in this progressive study. 5-point Likert scale ranging from 1"not at all" to 5 "extremely". Three scales measure

General Distress: depressive symptoms (12 items), anxious symptoms (11 items) and mixed symptoms (15 items) along with anxiety-specific (Anxious Arousal, 17 items) and depression-specific scale (Anhedonic Depression, 22 items). Higher scores reflect greater levels of symptomatology. The reported internal consistency for each scale is significant with coefficient alphas ranging from 0.78 to 0.92.

Statistical analyses

Descriptive statistics and statistical analyses were performed using the Microsoft office - excel. A basic protocol was developed and followed to perform clear statistics and highlight the associations and correlations if present between the variables (Figure 1).

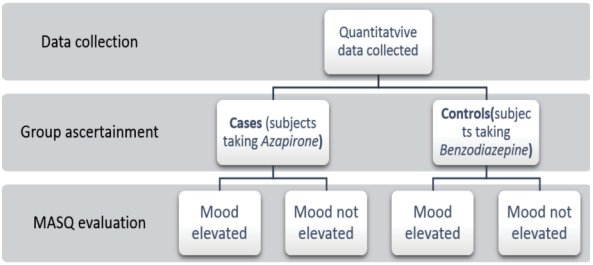

Figure 1: Study protocol

We summarized the characteristics of cases and two sets of controls using descriptive statistics. We performed conditional logistic regression to assess the association of mood elevation status with exposure of either drug interventions. ORs and their corresponding 95% CIs were presented after appropriate calculations made in MS-Excel 2021 updated edition using.

$$95\%\ CI = OR \pm 1.96 * \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}.$$

We also looked at differences between subgroups (ie, stratified by gender) although no formal comparisons were made because of the small sample sizes. As different subjects were followed prospectively, an independent unpaired t-test was performed to evaluate the variables and provide correlation between them. The authors used a chi-square (X^2) test to compare the groups and the Pearson Chi-square test of independence was calculated using:

$$\sum \chi^2_{i-j} = \frac{(0-E)^2}{E}$$

Where:
O Observed (the actual count of cases in each cell of the table)
E Expected value
χ^2 the cell Chi-square value
$\sum\chi^2$ Formula instruction to sum all the cell Chi-square values

$\chi 2i{-}jj{-}j$ is the correct notation to represent all the cells, from the first cell (i) to the last cell (j); in this case Cell 1 (i) through Cell 6 (j).

A Fisher's exact test was performed with a Cramer's phi to test the strength of association between the two variables.

RESULTS:

Descriptive statistics

Descriptive statistics are shown in Table 1. During this observational period from 1st August 2020 to 31st September 2020, a total of 96 patients were included in the study. The mean age of the participants was 21.2 years with higher number of female participants in the drug exposed groups.

	Treatment group				
Mood status			**Azapirone (Case)**	**Benzodiazepines (Control)**	**Total**
	Mood elevated	Observed number (O)	**26**	**29**	**55**
		Expected number (E)	***23.48***	***31.52***	
	Mood not elevated	Observed number (O)	**5**	**36**	**41**
		Expected number (E)	***17.51***	***23.49***	
	Total		**41**	**55**	**96**
	Treatment group (MALE)				
Mood status			**Azapirone (Case)**	**Benzodiazepines (Control)**	**Total**
	Mood elevated	Observed number (O)	**10**	**11**	**55**
		Expected number (E)	***6.81***	***14.19***	
	Mood not elevated	Observed number (O)	**2**	**14**	**41**
		Expected number (E)	***5.19***	***10.81***	
	Total		**12**	**25**	**37**
	Treatment group (FEMALE)				
Mood status			**Azapirone (Case)**	**Benzodiazepines (Control)**	**Total**
	Mood elevated	Observed number (O)	**16**	**18**	**55**
		Expected number (E)	***10.95***	***23.05***	
	Mood not elevated	Observed number (O)	**3**	**22**	**41**
		Expected number (E)	***8.05***	***16.95***	
	Total		**25**	**12**	**37**

Table 1: Contingency table with showing the observed and expected counts (number of patients) with and without mood elevation per treatment group. Assuming that the probability of mood upliftment is independent of the group allocation (null hypothesis), 23.48 patients with mood elevation would be expected in each group (given a total of 55 patients who had a better mood and equal sample size in both groups). Pearson χ^2 test compares observed to expected frequencies.

The mean age of the participants was 21.2 and the sample was comprised of 61.5% females (N=59) and 38.5% males (N=37). There was no significant gender difference in MASQ scores, t (94) = 0.36, p = 0.37, despite women (M=185.88, SD=100.38) attaining lower scores than men (M=193.49, SD=100.13). A total of 57.3% (N=55) of subjects from both: case and control groups showed significant mood elevation with a MASQ score <194, t (94) = -25.35, p<0.01 [Table 4].

Parameters	Groups	N	Mean +- SD	p-value
Mood elevated	Case (AZP)	26	95.15 ±12.69	<0.01
	Control (BZD)	29	120.52 ± 31.16	
Mood not elevated	Case (AZP)	4	264.25 ± 56.44	0.14
	Control (BZD)	36	299.08 ±43.57	
GENDER ADJUSTED - MALE				
Mood elevated	Case (AZP)	10	101.30 ± 15.22	<0.05
	Control (BZD)	11	120.09 ± 28.65	
Mood not elevated	Case (AZP)	2	308 ±32.53	0.4
	Control (BZD)	14	300.64 ± 37.56	
GENDER ADJUSTED - FEMALE				
Mood elevated	Case (AZP)	16	91.31 ± 6.4	<0.01
	Control (BZD)	18	120.78 ± 33.41	
Mood not elevated	Case (AZP)	3	254.33 ± 62.08	0.08
	Control (BZD)	22	298.09 ± 47.83	

Table 4: Comparison Of Mood Elevation In Subjects Treated With Azp (case) And Bzd (control) Along With Gender Wise Comparison.

83.8% (N=26) of patients in the case group (Azapirone group [N = 31]) treated with buspirone showed mood elevation (MASQ score < 194) along with life satisfaction, t (28) = -14.30, p <0.01. The traditional interventional modality for GAD utilized in this study was benzodiazepine (control group N=65) and the subjects were treated with a short acting drug: alprazolam. The control group showed significant mood upliftment in only 44.61% (N=29/65) of subjects (t (63) = -18.56, p < 0.01) as compared to 83.8% (N=26/31] of the case group.

However, there was no significant difference seen with higher scores (MASQ > 195) which signified absence of mood upliftment or failure to treat the patient's primary pathology, i.e., anxiety, t (39) = 1.09, p=0.14 [Table 4].

A chi-square test of independence [Table 3] was performed to examine the relation between drugs used in the case and control groups to manage GAD and the upliftment of mood and mental well-being as parameters. The relation between these variables was significant, χ^2(1, N=96) = 16.07, p<0.01. Subjects in the case group, i.e., patients taking buspirone were more likely than the patients taking alprazolam to achieve a better state of mental health.

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Factors		Case *N* (%)		Control *N* (%)		*P*-value	χ^2 (d.f.=1)	Cramer's phi (φc)
		Observed	*Expected*	Observed	*Expected*			
Mood status	Elevated	26(27.08)	*23.48*	29(30.21)	*31.52*	<0.01	16.07	0.409
	Not Elevated	5(5.21)	*17.51*	36(37.5)	*23.49*			
GENDER ADJUSTED - MALE								
Mood status	Elevated	10(27.03)	*6.81*	11(29.73)	*14.19*	<0.05	5.11	0.372
	Not Elevated	2(5.4)	*5.19*	14(37.84)	*10.81*			
GENDER ADJUSTED - FEMALE								
Mood status	Elevated	16(27.12)	*10.95*	18(30.51)	*23.05*	<0.01	8.11	0.371
	Not Elevated	3(5.08)	*8.05*	22(37.29)	*16.95*			

Table 3: Extended contingency table indicating a relationship between elevated mood status in the case and control groups with gender wise distribution.

Odds of significant mood upliftment and better mental health outcome were higher in those subjects taking buspirone, compared with those taking alprazolam ($p<0.01$, $OR = 6.45$; *95% CI*, 2.2 – 18.9) [Table 2].

FACTORS		Case *N* (%)	Control *N* (%)	*P*-value	OR	95% CI
Mood status	Elevated	26(27.08)	29(30.21)	<0.01	1	Reference
	Not Elevated	5(5.21)	36(37.5)		6.456	2.2, 18.9
GENDER ADJUSTED - MALE						
Mood status	Elevated	10(27.03)	11(29.73)	<0.05	1	Reference
	Not Elevated	2(5.4)	14(37.84)		6.363	1.14,35.23
GENDER ADJUSTED - FEMALE						
Mood status	Elevated	16(27.12)	18(30.51)	<0.01	1	Reference
	Not Elevated	3(5.08)	22(37.29)		6.518	1.63,25.95

Table 2: Estimated impact on mood upliftment and a positive mental status in subjects with generalized anxiety disorder treated with AZP (cases) with gender adjustment.

Gender adjusted statistics

The genders in the case and the control group were adjusted and segregated in order to remove any biases. Primarily, the mood elevation of the case and control groups when segregated based on their gender with lower MASQ scores showed significance. The 10 participants who received the drug intervention from the case group (buspirone) (M=101.30, *SD* = 15.22) compared to the 11 participants in the control group (*M*=120.09, *SD* = 28.65) demonstrated significantly better mental health status, t (19) = 1.85, p = 0.04. Similarly, the 16 female participants who received the drug intervention (*M*=91.31, *SD*= 9.40) compared to the 18 female participants in the control group (*M*=120.78, *SD*=33.41) demonstrated significantly better mood upliftment, t (32) = 3.41, p <0.01 [Table 4].

Participants who felt the same or did not have any sort of mood elevation underwent this subgroup analysis [Table 4]. There was no significant relationship between higher MASQ scores (>195) i.e., patients failing to achieve mood elevation in either the case or the control groups. In the male sub-group, 2 subjects in the case group (*M*=308, *SD*=32.53) compared to the 14 subjects in the control group (*M*=300.64, *SD*=37.55) did not demonstrate significantly better mood elevation, t (14) =-0.26, p=0.4. Similarly, 3 female subjects from the case group (*M*=254.33, *SD*=62.08) when compared to the 22 female subjects in the control group (*M*=298.09, *SD*=47.83) showed insignificant presence of mood elevation, t (23) =1.44, p=0.08.

A chi-square of independence [Table 3] showed that there is a significant relationship of the drug intervention over mood when adjusted for gender. The proportion of subjects (N =37 males) who reported being mentally uplifted with a better mood was likely due to the drug used in the case group, $\chi^2(1, N = 37) = 5.11$, p=0.02. The proportion of females (N=59) as a part of the study's subgroup analysis showed similar significant relationship, $\chi^2(1, N = 59) = 8.11$, p<0.01.

Odds of significant mood upliftment and better mental health outcome were higher in those subjects taking buspirone, compared with those taking alprazolam even after gender adjustment: male subjects ($p<0.05$, $OR = 6.36$; *95% CI*, 1.14 – 35.23); female subjects ($p<0.01$, $OR = 6.52$; *95% CI*, 1.63 – 25.95) [Table 2].

DISCUSSION:

The current study utilized the MASQ scoring system to analyze patients with generalized anxiety disorders, i.e., the participants of either group suffering from anxiety disorder for more than 6 months. It proves the presence of mood elevation in patients taking azapirones despite the lowering effect on 5-HT levels of the drug known to be associated with mood upliftment. The evaluation was done and then scores more than 195 (median value) were considered to either have remnant symptoms of anxiety or no mood elevation. The purpose of the study was to highlight the paradoxical presence of mood elevation in patients taking azapirone class of anxiolytics despite its opposite pharmacodynamic properties on the molecular pathophysiology of mood. Results of this study correspond well with the molecular basis of the drug as mentioned by many studies. Decreased serotonergic neurotransmission is associated with a number of mood disorders, e.g., bipolar illness, panic disorder, major depression and suicide. Azapirones are a delayed acting class of drugs used for anxiety without the potential of abuse as seen in benzodiazepines. Long-term administration of novel anxiolytics such as buspirone, 5-HT_{1A} somatodendritic autoreceptors become desensitized. Attenuation of 5-HT_{1A} somatodendritic auto receptor sensitivity and function results in an increase in serotonergic neuronal firing rate and 5-HT neurotransmission, and is believed to contribute to the therapeutic effect of antidepressant drugs. The aim of this study was to bring emphasis on the contradiction associated with azapirones as anxiolytics on mental health well being despite the depression of serum 5-HT levels. It is important to underscore that 5-HT's effect on mood although elevates it yet occurs in the context of multiple other neuromodulatory systems such as noradrenaline, dopamine and neurotrophins that may have distinct yet related effects on mood regulation, and which have their own developmental trajectories. [7].

The physiological contradiction that depression and chronic anxiety are more common in women than men, showcases a reduced baseline of endogenous serotonergic neurotransmission in women. [8] However, the primary outcome of the study did not have an association with endogenous 5-HT levels in females. On further subgroup analysis of the primary outcome, it showed that women had significant mood elevation when treated with azapirones depicting a greater availability of 5-HT transporter in females, in agreement with the findings mentioned by Staley JK, et al. [9]

One of the undocumented outcomes of this study was that many patients opted for buspirone as their primary intervention due to a combined action over their anxiety symptoms and a concurrent feeling of upliftment. This was found in patients with newly diagnosed GAD and on subjects who were earlier treated with benzodiazepines. This study was first in its kind despite the already understood depressed levels of 5-HT in patients using buspirone. The study has potential in reducing empirical utilization of benzodiazepines to treat chronic anxiety disorders as it indicates an ongoing better mental status (mood related) as an additional benefit of azapirones along with zero potential of abuse, as seen with benzodiazepines.

The empirical results reported herein should be considered in the light of some limitations. The generic limitation presented here was the undersized sample size of the population chosen as cases and controls. The smaller sample size can lead to an inability to attribute causality irrespective of the observational evidence. Another limitation of the study was that there were no serum 5-HT investigations done to confirm the depressed 5-HT neurotransmission and decreased levels after using buspirone. The focus shifts on the pharmacokinetic / pharmacodynamic of the drug which points towards a molecular mystery yet to deciphered. Further studies in future are needed with a larger sample size in order to confirm the findings from this study.

CONCLUSION

Patients belonging to the azapirone class of anxiolytic had a better post drug exposure and unbiased selection than compared to the group consuming benzodiazepines regardless of their mutual therapeutic role towards anxiety. The female subgroup had a stronger predominance towards lower MASQ scores, indicating a generalized uplifted mood. Lastly, the pharmacologic controversy which was the primary endpoint of our study was reinforced as a paradoxical case of mood elevation upon lowering of serum serotonin levels and its neurotransmission.

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