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A MATHEMATICAL PROBABILITY MODEL USING FOR THE FLUVOXAMINE REDUCES RESPONSIVENESS OF HPA AXIS IN ADULT FEMALE BPD PATIENTS WITH A HISTORY OF SUSTAINED CHILDHOOD ABUSE

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ABSTRACT

The Weibull Generalized family of distributions was used to propose a three-parameter probability model Weibull exponential distribution. The proposed model's mathematical property was discussed. The aim of this study was to see how much ACTH and Cortisol secreted in response to the CRH/DEX test before, during, and after 6 and 12 weeks of fluvoxamine treatment in female borderline patients with and without history of sustained childhood abuse. For the two hormones described above, we plotted the cumulative distribution function, probability vacuity function, failure rate, and responsibility function of the proposed model. We discovered that BPD patients with a history of prolonged childhood abuse have the greatest reduction in ACTH and cortisol, and that fluvoxamine therapy decreases the hyper responsiveness of the HPA axis. Finally, we conclude that the proposed model's responsibility feature is well matched to the application component, and the conclusion is compared to a medical study. This paper would be extremely helpful in the fields of insurance, engineering, and medicine, as well as economics and finance.

Keywords: BPD, fluvoxamine, childhood abuse, HPA, ACTH Cortisol, Weibull exponential distribution.

1. INTRODUCTION

In the fields of insurance, engineering, medicine, economics, and finance, a variety of traditional theoretical distributions have been found to be useful. To this end, a number of well-known authors have proposed methods for generating new families of distributions [2] for more details.

The exponential distribution is a well-known continuous probability model that has been used for a variety of purposes, including life research. The beta exponential distribution was created as a result of attempts to make the exponential distribution more flexible. Exponentiated exponential distribution [6] and Generalized exponential distribution are two types of exponential distributions. exponential distribution of Kumaraswamy [3], inverse exponential distribution, and so on. In the remainder of this article, the same exponential distribution will be used as the beginning distribution. The Weibull Generalized family of distribution is one of the many families of distributions that we are interested in in this paper.

The explanation for this is that three distinct types of distributions of this kind have been found.[1] [2] .Let T denote a random variable ever follows a Weibull distribution by parameters c and γ, the cumulative vacuity function of the Weibull –X family due to [1] is obtained from

$$F(X)= \int_{0}^{-log\,(1-G(X))} r(t)dt \qquad -------(1)$$

Therefore in [1]

$$r(t) =[\frac{c}{\gamma}][\frac{t^{c-1}}{\gamma}] \quad e^{[\frac{-1}{\gamma}^{c}]} \quad t \geq 0\ ,\ c> 0,\gamma>0 \qquad -------(2)$$

Where c is the condition parameter and $\gamma$is the scale parameter

The corresponding probability vacuity function of the Weibull –X family due to [1] is given by

$$f(x) = [\frac{c}{\gamma}]\frac{g(x)}{1-G(x)}[\frac{-log(1-G(X))^{c-1}}{\gamma}] \quad e^{[\frac{-log\,(1-G(X)^{c}}{\gamma}]} \qquad -------(3)$$

$$t\geq 0\ ,\ c> 0,\ \gamma> 0$$

Where g(x) is the pdf of the beginning distribution and G(x) is the cdf of the beginning distribution The cdf of another form of the Weibull generalized family of distribution due to [2] is given by

$$F(X)= \int_{0}^{\frac{G(x)}{1-G(x)}} \alpha\beta t^{\beta-1}e^{-\alpha t^{\beta}} \qquad -------(4)$$

Eq. (4) was further solved to give (5)

$$F(x) = 1 - exp\,[[\frac{-\alpha G(x)^{\beta}}{1-G(x)}]\ ] \qquad -------(5)$$

$$x \geq 0\ ,\ \alpha> 0,\ \gamma>\ 0$$

The corresponding probability vacuity function of the Weibull –G family due to **[2]** is given by

$$f(x) = \alpha\beta g(x)\frac{G(x)^{\beta-1}}{(1-G(x))^{\beta+1}} exp\,[[\frac{-\alpha G(x)^{\beta}}{1-G(x)}]\ ] \qquad -------(6)$$

The remainder of this paper is structured as follows: section 2 describes the proposed Weibull exponential distribution's pdf and cdf, then basic mathematical properties of the proposed distribution model.

2. MATHEMATICALMODEL

Weibull ExponentialDistribution

Let the exponential distribution to be the parent distribution with a pdf and cdf respectively given by

$$g(x) = \lambda e^{-\lambda x} x> 0,\ \lambda>0 \qquad -------(7)$$

$$G(x) = 1 - e^{-\lambda x} x> 0,\ \lambda>0 \qquad -------(8)$$

$\lambda$is the scaleparameter

To derive the cdf of the Weibull exponential distribution, Eq. (8) is inserted into Eq. (5)

$$F(x) = 1 - exp\,[[\frac{-\alpha(1-e^{-\lambda x})^{\beta}}{e^{-\lambda x}}]\ ] \qquad -------(9)$$

Eq. (9) can further be simplified to give (10)

$$F(x) = 1 - exp\,[[-\alpha(e^{\lambda x} - 1)]^{\beta}] \qquad -------(10)$$

$$x> 0,\ \lambda> 0\ \alpha> 0\ and \beta> 0$$

The resembling pdf is obtained by

$$f(x)=\alpha\beta\lambda e^{-\lambda x}(1-e^{-\lambda x})^{\beta-1} \quad exp[[(e^{-\lambda x})^{\beta+1}(e^{-\lambda x}) \quad]\,]-------(11)$$

$For x>0,\ \lambda>0\ \alpha>0\ and \beta>0$

The expression is Eq. (11) can further be expressed as Eq.(12)

$$f(x)=\alpha\beta\lambda(1-e^{-\lambda x})^{\beta-1}exp[x\beta\lambda-\alpha(e^{\lambda x}-1)^{\beta}] \qquad -------(12)$$

RESPONSIBILITY ANALYSIS

The responsibility function is mathematically given by

$$S(x) = 1 - F(x)$$

In this case F(x) is the cdf of the Weibull exponential distribution as defined in Eq. (12).Therefore the responsibility function of the proposed model is given by

$$S(x)=exp[[-\alpha(e^{\lambda x} - 1)]^{\beta} \qquad -------(13)$$

$For x>0,\ \lambda>0\ \alpha>0\ and \beta>0$

The failure grade is mathematically given by

$$h(x) = \frac{f(x)}{1 - F(x)}$$

Therefore the resembling failure rate for the Weibull exponential distribution is expressed as follows

$$h(x) = \frac{\alpha\beta\lambda(1 - e^{-\lambda x})^{\beta-1}exp\,[x\beta\lambda - \alpha(e^{\lambda x} - 1)^{\beta}]}{exp[[-\alpha(e^{\lambda x}-1)]\beta]} \qquad -------(14)$$

3. APPLICATION

ACTH and Cortisol Response Pre/Post- Fluvoxamine:

After 6 or 12 weeks of fluvoxamine therapy, there were no major improvements in mean afternoon beginning cortisol and ACTH levels. Fluvoxamine therapy, on the other hand, was linked to a substantial and sustained reduction in the mean AUC of the ACTH and cortisol responses to DEX/CRH challenge: The cortisol concentration time curve's mean AUC fell from 85.3 (SD=110.7) to 16.65.(SD= 44.42); (t=3.77, df=29, p=0.001), and mean AUC of the ACTH concentration time curve from 8.77(SD = 9.21) to 2.21 (SD=5.18); (t=3.70, df=29p=0.001).

Covariates: Childhood Abuse, MDD, andPTSD:

Stepwise backward tests of covariance is used to see whether the reduction of HPA axis responsiveness by fluvoxamine treatment is reflected more in BPD subjects with a history of prolonged childhood violence and if this effect is influenced by comorbid abuse and whether this effect is affected by comorbid PTSD or MDD. There were no differences in mean cortisol and ACTH levels at the start of the afternoon. Changes in the AUCs of the cortisol and ACTH responses to the DEX/CRH test, on the other hand, were substantially influenced by a history of prolonged childhood violence, but not by psychiatric comorbidity.The mean AUC ACTH response for those who experienced sustained childhood abuse fell from 12.70 (SD=10.41) to 2.37 (SD=5.82), while the mean AUC ACTH response for those who experienced no or incidental childhood abuse fell from 3.63 (SD=3.19) to 2.00 (SD=4.43) (F(1.28)=7.19, p=0.012; see also Figure 3.3). The mean AUC cortisol response for those who experienced prolonged childhood abuse decreased from 113, 2 (SD=121, 0) to 13, 9 (SD=30.7), while the mean AUC cortisol response for those who experienced no or incidental childhood abuse decreased from 48.9 (SD=87.0) to 20.2 (SD=59.1) (F (1.28) = 4.08, p=0.058; see also Figure 3.4).

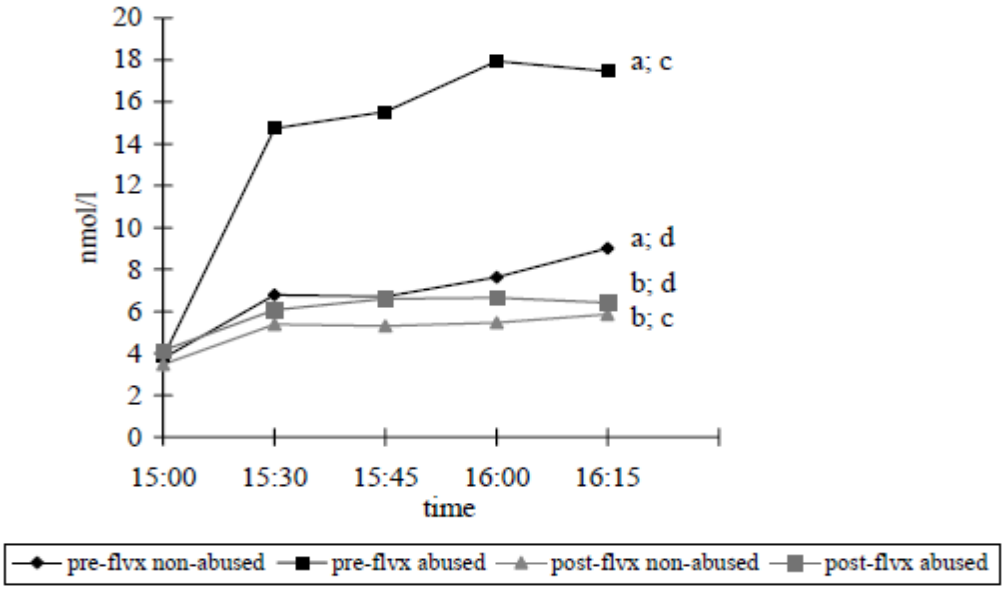


Fig 3.2(a) Pre and post fiuvoxamine therapy, concentration time curves of ACTH responses to DEX/CRH challenge for abused (n=17) and non-abused (n=13) BPD subjects. Student's t-test for self-dependent samples of mean ACTH AUCs of abused subjects before fluvoxamine treatment (a) t= 3.390, df =28, p= 0.005 and after fluvoxamine treatment (b) t=.199, df =28, p= 0.84. The mean AUC of ACTH was tested using the Student's twain t-test.pre vs post fluvoxamine treatment fot the abused and not abused subjects (c) t= .-3.80, df =16 ,p= 0..002and(d) t= .1.61, df =12 ,p= 0.134 respectively

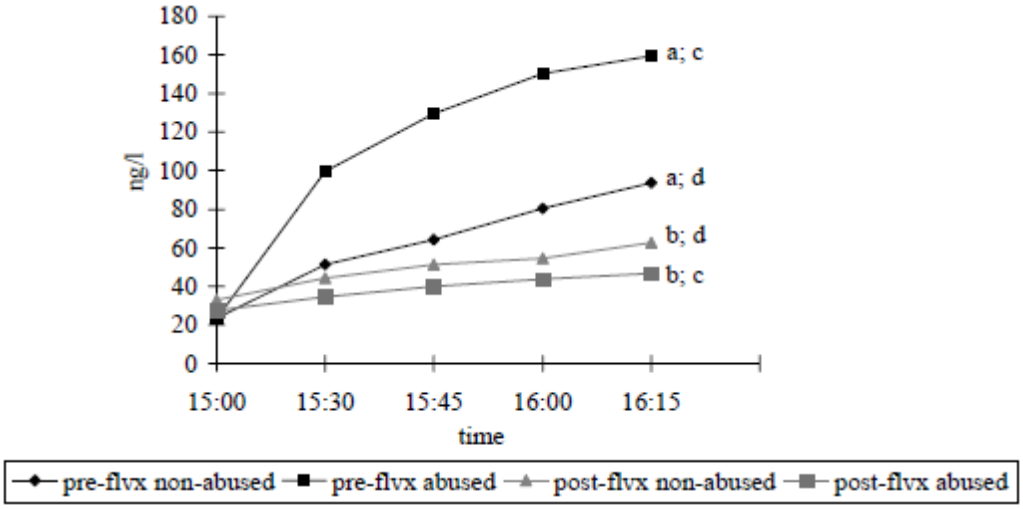


Fig 3.2(b) Cortisol responses to a DEX/CRH challenge for abused (n=17) and non-abused (n=13) BPD subjects before and after fiuvoxamine therapy. Pre-fluvoxamine treatment (a) t = 1.69, df =27.93,p= 0.10; post-fluvoxamine treatment (b) t = 0.352, df =16.93,p= 0.73. The mean AUC was tested using the Student's twain t-test pre vs post fluvoxamine treatment fot the abused and not abused subjects (c) t = 3.57, df =16 ,p= 0..001 and (d) t= 1.75, df =12 ,p= 0.106respectively

Time Frame of the Fluvoxamine Effect on the HPA Axis

After 6 weeks of fluvoxamine treatment (n=14) and 12 weeks of fluvoxamine treatment (n=16), the AUC of ACTH response after DEX/CRH challenge decreased from 8.99 (SD=9.70) to 2.60 (SD=4.07) and from 8.57 (SD=9.08) to 1.87 (SD=6.10), respectively.

Since both groups experienced the same decrease, there was no statistically significant group by time effect (F (1.28) = 0.007, p=0.933), meaning that fluvoxamine is more likely to have an effect in the first 6 weeks of care.

4. DISCUSSION

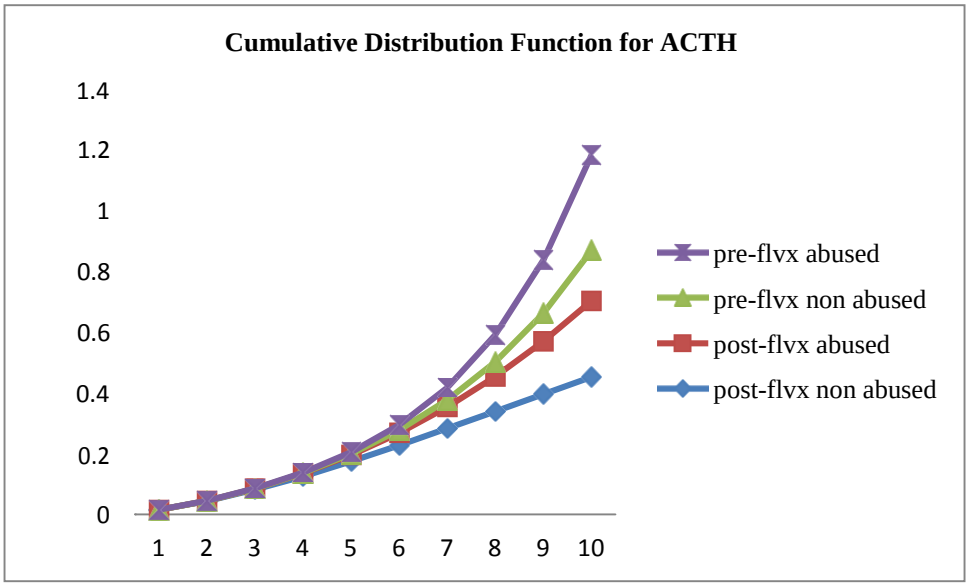
In chronically abused BPD subjects, fluvoxamine treatment was linked to a substantial and robust reduction in ACTH and cortisol responses to the combined DEX/CRX challenge test. BPD patients with no or minor childhood violence had low ACTH and cortisol responses to the DEX/CRX challenge before and after treatment. The effect of fluvoxamine on ACTH and cortisol response to the DEX/CRH test in these BPD subjects was unaffected by the existence of a comorbid diagnosis of MDD or PTSD. The comparison of the ACTH and cortisol responses after 6 and 12 weeks of fluvoxamine treatment suggests that the decrease in ACTH and cortisol response is already known after 6 weeks of treatment. The reduction in ACTH and cortisol responses to the DEX/CRH test after fluvoxamine treatment in chronically childhood abused BPD subjects may be due to a decrease in their enhanced CRH/AVP drive.

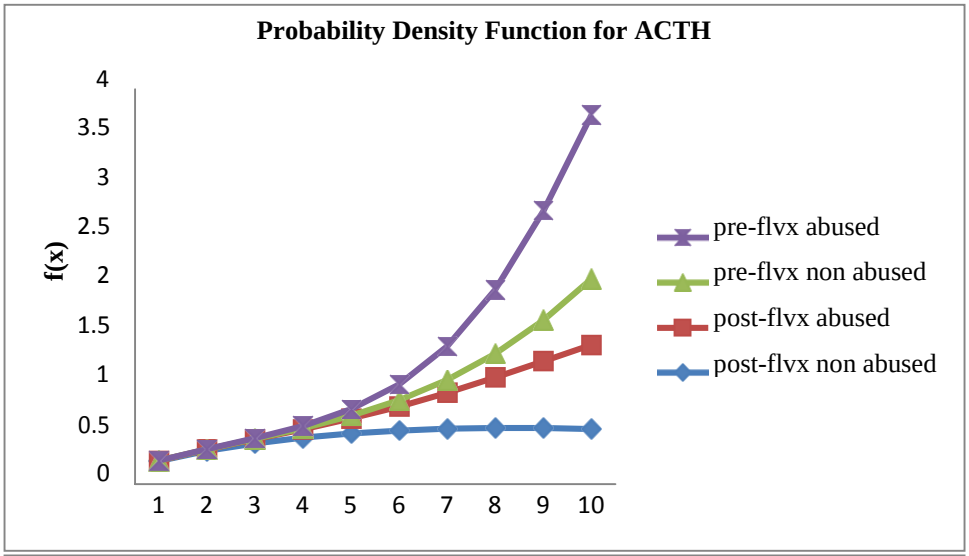
Preclinical studies have shed light on how the effects of childhood trauma and fluvoxamine on the HPA axis develop. Early life stressors, such as maternal neglect, tended to increase the HPA axis' responsiveness into adulthood. The effect of maternal deprivation resulted in altered expression of the hippocampal mineralo (MR) and glucocorticoid receptor (GR) sites, which may explain why HPA responsiveness was increased [5]. Early stress was found to increase the number of hypothalamic CRH neurons and the expression of CRH and AVP m-RNA in other studies**[4].**

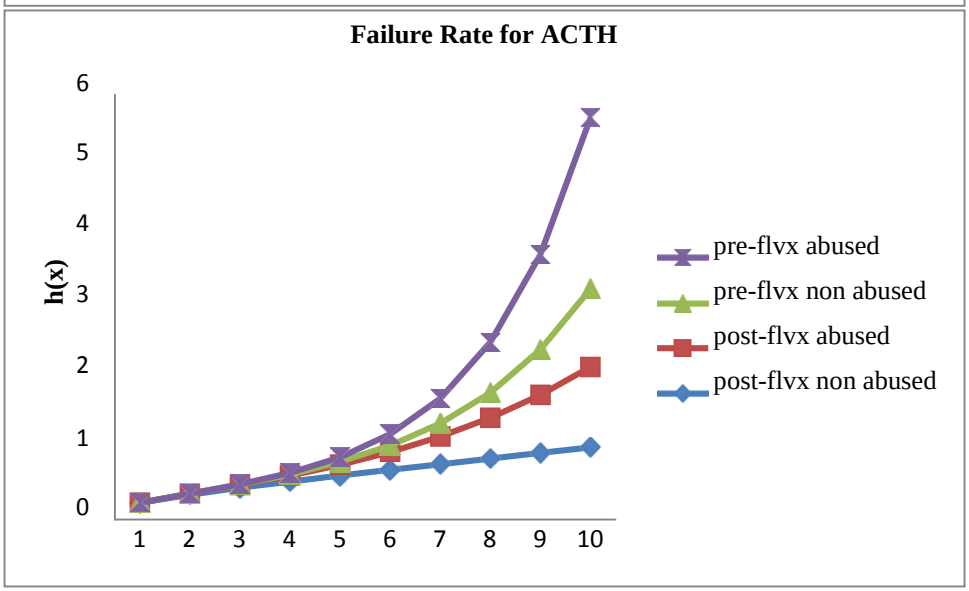
In pituitary corticotrophs, increased AVP/CRH release is likely to increase the expression of pro-opiomelanocortin (POMC) synthesis and the release of its peptide product ACTH.Preclinical research on the effects of chronic antidepressant administration show that a decrease in HPA-axis activity is a typical final pathway of antidepressant effects, but that antidepressants have different pharmacological efficacy on different HPA-axis levels and receptor subsystems. Depending on the type of drug, tricyclic antidepressants and the SSRI fluoxetine are likely to increase either GR or MR m-RNA expression in the hippocampus. They are thought to re-establish the inhibitory tone on the PVN in the hypothalamus as a result of the rise in hippocampal MRs and GRs.

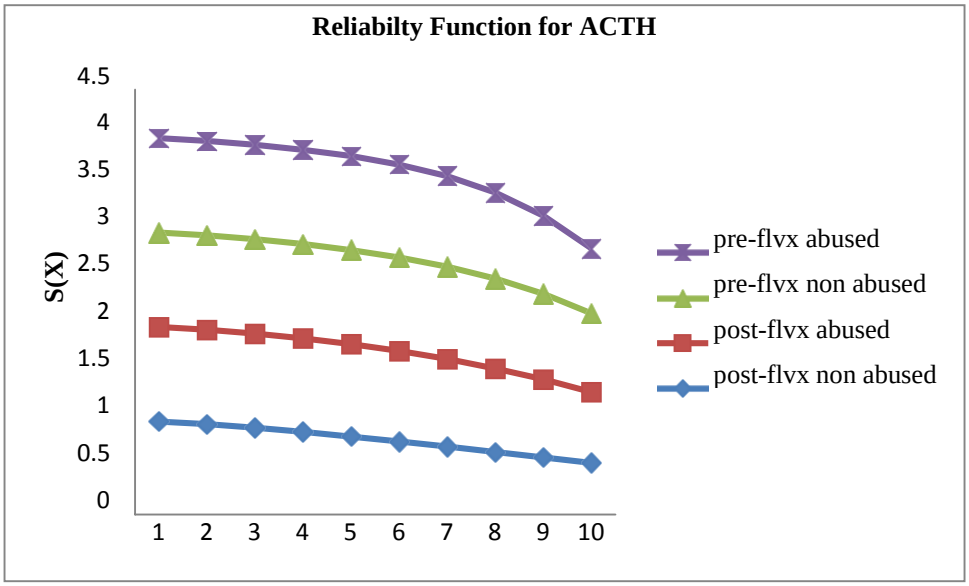
According to this hypothesis, after fluoxetine therapy, CRH m-RNA in the hypothalamic PVN and CSF CRH, as well as AVP, are reduced. Another (hypothetical) mechanism of SSRI action on the HPA axis may be of interest in this paperIn the event of tension, the PVN's CRH neurons and the LC's locus coruleus (LC) maintain a positive feedback loop . The firing rate of noradrenergic neurons in the LC is decreased after long-term SSRI treatment . This is supposed to affect the hypothalamic CRH neurons and, as a result, the release of ACTH secretagogs.

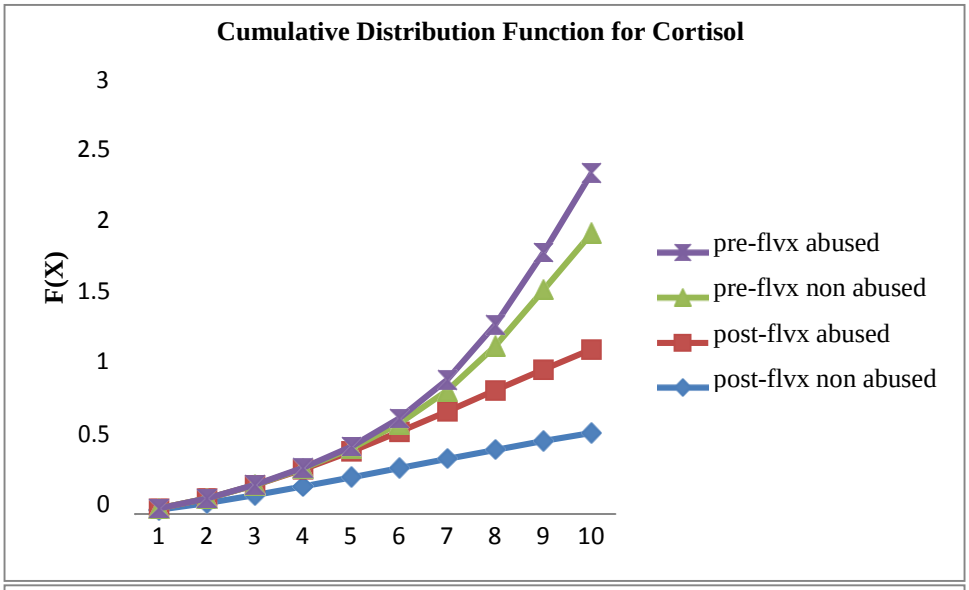
5. MATHEMATICALRESULTS

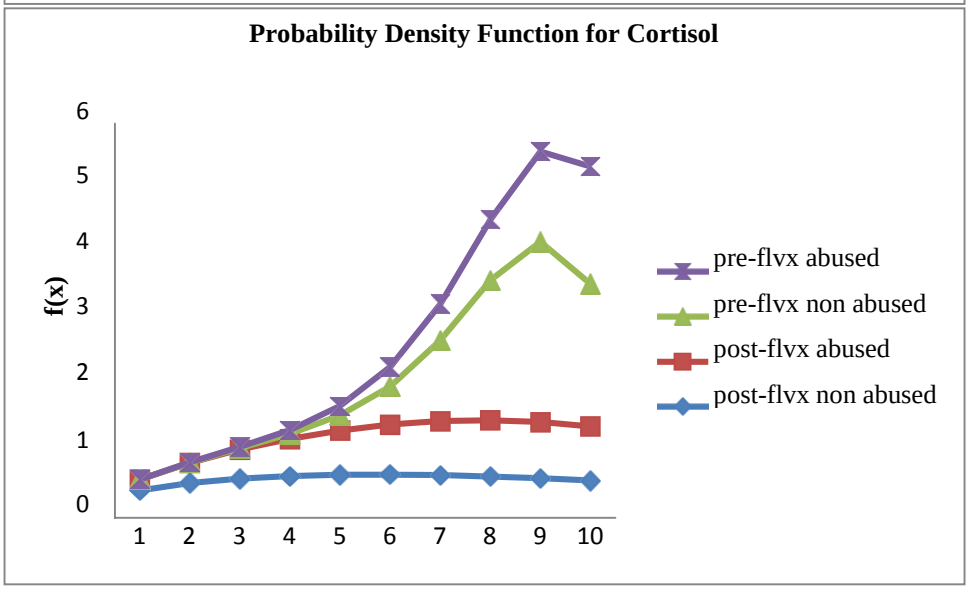


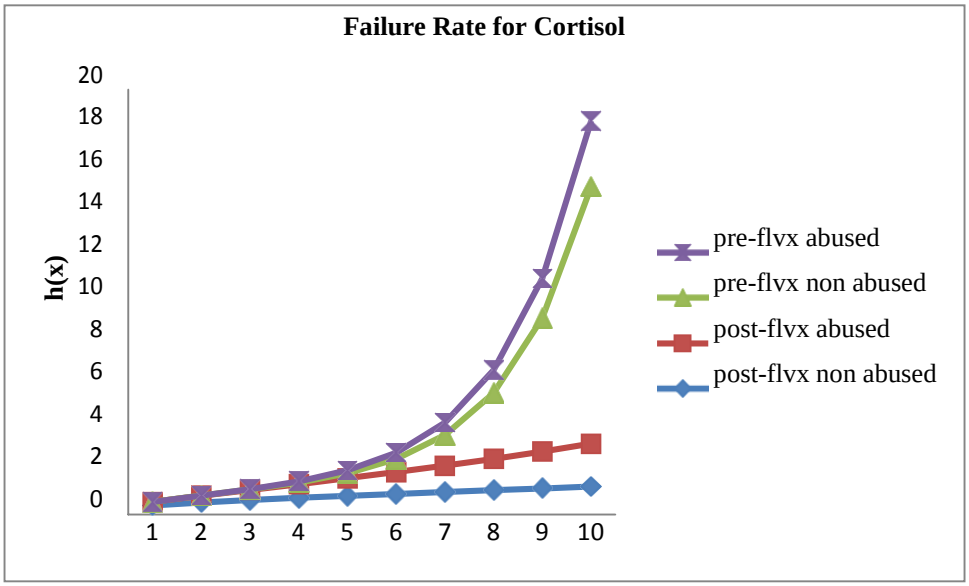

Probability Density Function for ACTH
f(x)
4
3.5
3
2.5
2
1.5
1
0.5
0
1 2 3 4 5 6 7 8 9 10
pre-flvx abused
pre-flvx non abused
post-flvx abused
post-flvx non abused

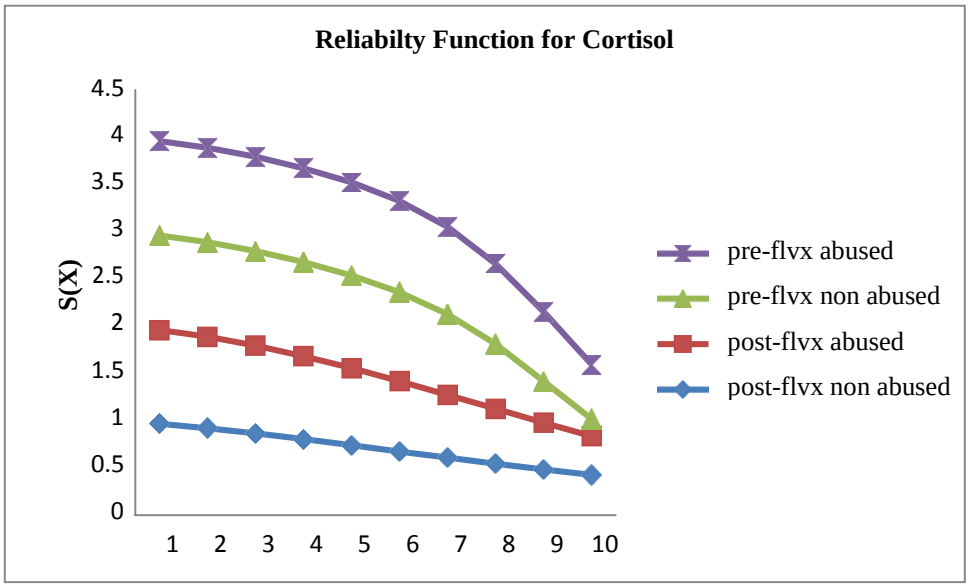

Failure Rate for ACTH
h(x)
6
5
4
3
2
1
0
1 2 3 4 5 6 7 8 9 10
pre-flvx abused
pre-flvx non abused
post-flvx abused
post-flvx non abused


Reliabilty Function for ACTH
S(X)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
1 2 3 4 5 6 7 8 9 10
pre-flvx abused
pre-flvx non abused
post-flvx abused
post-flvx non abused


Cumulative Distribution Function for Cortisol
F(X)
3
2.5
2
1.5
1
0.5
0
1 2 3 4 5 6 7 8 9 10
pre-flvx abused
pre-flvx non abused
post-flvx abused
post-flvx non abused


Probability Density Function for Cortisol
f(x)
6
5
4
3
2
1
0
1 2 3 4 5 6 7 8 9 10
pre-flvx abused
pre-flvx non abused
post-flvx abused
post-flvx non abused


Failure Rate for Cortisol
h(x)
20
18
16
14
12
10
8
6
4
2
0
1 2 3 4 5 6 7 8 9 10
pre-flvx abused
pre-flvx non abused
post-flvx abused
post-flvx non abused



6. CONCLUSION

The Weibull exponential distribution with three parameters has been successfully described. The proposed model's mathematical property was thoroughly debated, and it was concluded that the Weibull exponential distribution is more stable than the exponential distribution. For ACTH and cortisol hormones, we plotted the cumulative distribution function, probability vacuity function, failure rate, and obligation function of the proposed model. We discovered that BPD patients with a history of prolonged childhood abuse have the greatest reduction in ACTH and cortisol, and that fluvoxamine therapy decreases the hyper responsiveness of the HPA axis.Finally, we conclude that the proposed model's obligation feature is well suited to the application portion, and the conclusion is compared to a medical study. This paper would be extremely helpful in the fields of insurance, engineering, and medicine, as well as economics and finance.

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