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: A three parameter probability model Weibull exponential distribution was proposed using the Weibull Generalized family of distributions. A mathematical property of proposed model was discussed. The aim of this paper was to evaluate the secretion levels in ACTH and Cortisol responses to the CRH/DEX test before and after 6 and 12 weeks of fluvoxamine treatment in female borderline patients(borderline personality disorder BPD) with and without history of sustained childhood abuse. We have plotted cumulative distribution function, probability density function, Failure rate and reliability function of proposed model for above mentioned two hormones. Using these mathematical reports we found that the BPD patients with a history of sustained childhood abuse showed the strongest reduction in ACTH and cortisol and fluvoxamine treatment reduces the hyper responsiveness of the HPA axis. Finally we conclude that reliability function of proposed model is well fitted with application part and conclusion is compared with medical report. This paper will be very useful in the field of insurance, engineering and medicine, economics and finance.

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

1. INTRODUCTION

A number of standard theoretical distributions have been found to be useful in the fields of insurance, engineering, medicine, economics and finance. However generalizing these standard distributions has produced several compound distributions that are more flexible compared to the base line distributions. To this end several attempts have been made by notable authors to propose methods for generating new families of distributions **[2]** for more details.

Exponential distribution is a well known continuous probability model which has been identified as a life testing model among many other applications. Attempts to increase the flexibility of the exponential distribution gave rise to the beta exponential distribution**. [10]** exponentiated exponential distribution **[6]** ,Generalized exponential distribution **[7]** kumaraswamy exponential distribution**[3]** , inverse exponential distribution and so on. This same exponential distribution will be considered as the baseline distribution in the rest of this article.

Out of the several families of distributions of interest to us in this paper is the Weibull Generalized family of distribution. The reason is that about three different forms of such class of distribution have been observed **[1] [2] [11].**

Let T denote a random variable that follows a Weibull distribution with parameters c and γ , the cumulative density 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]

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

Where c is the shape parameter and γ is the scale parameter

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

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

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

Where g(x) is the pdf of the baseline distribution and G(x) is the cdf of the baseline 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)

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

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

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

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

The rest of this paper is organized as follows; section-2 defines the pdf and the cdf of the proposed Weibull exponential distribution followed by basic mathematical property of the proposed distribution model

2. MATHEMATICAL MODEL

2.1 Weibull Exponential Distribution

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

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

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

λ is the scale parameter

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

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

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

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

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

The corresponding pdf is obtained by

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

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

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

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

2.2 Reliability Analysis:

The reliability 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 reliability function of the proposed model is given by

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

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

The failure rate is mathematically given by

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

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

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

3. APPLICATION

3.1 ACTH and Cortisol Response Pre/Post- Fluvoxamine :

No significant overall changes in mean afternoon baseline cortisol and ACTH baseline levels were detected after 6 or 12 weeks of fluvoxamine treatment. However, fluvoxamine treatment was associated with a significant and robust decrease of the mean AUC of the ACTH and cortisol response to DEX/CRH challenge: Mean AUC of the cortisol concentration time curve decreased 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=29 p=0.001).

3.2 Covariates: Childhood Abuse, MDD, and PTSD:

Regarding the question as to whether the reduction of the responsiveness of the HPA axis by fluvoxamine treatment is expressed more in BPD subjects with a history of sustained childhood abuse and whether this effect is affected by comorbid abuse and whether this effect is affected by comorbid PTSD or MDD, stepwise backward analyses of covariance have been performed. This revealed no effects for changes in mean cortisol and ACTH afternoon baseline levels. However, changes in AUCs of the cortisol and ACTH response to the DEX/CRH test were significantly dependent on a history of sustained childhood abuse, but not on the various forms of psychiatric comorbidity. Mean AUC ACTH response for those subjects with sustained childhood abuse dropped from 12.70 (SD=10.41) to 2.37 (SD=5.82), while for those subjects with no or incidental childhood abuse the mean AUC ACTH response dropped 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). Mean AUC cortisol response for those subjects with sustained childhood abuse dropped form 113, 2 (SD=121, 0) to 13, 9 (SD=30.7), while for those subjects with no or incidental childhood abuse the mean AUC cortisol response dropped 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).

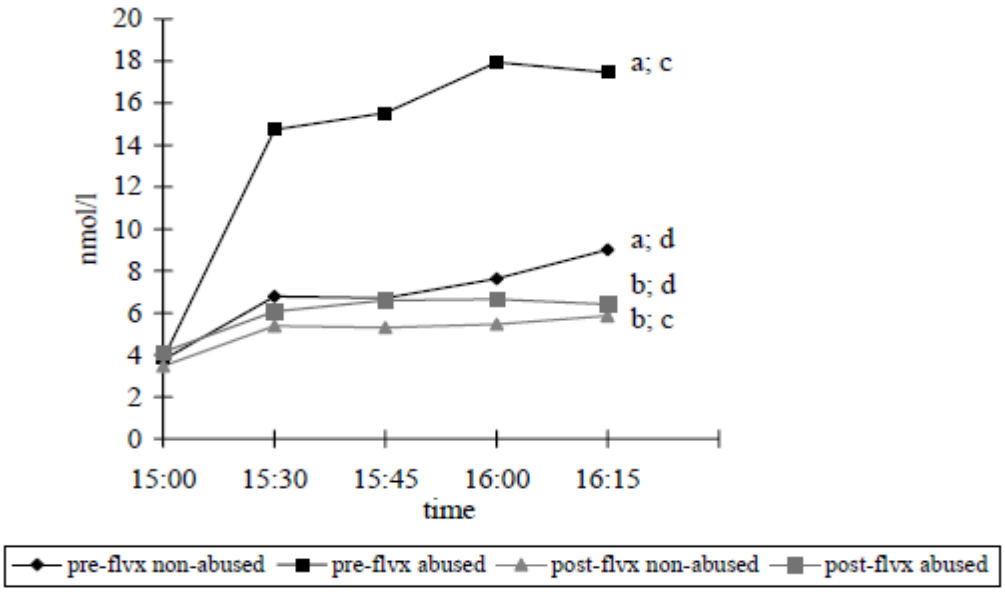


Fig 3.2(a) Concentration time curve of ACTH responses to DEX/CRH challenge pre and post fiuvoxamine treatment for abused (n =17) and not abused (n=13) BPD subjects. Student's t-test for independent samples of mean AUCs of ACTH of the abused subjects pre-fluvoxamine treatment (a) t= 3.390, df =28 ,p= 0.005 and post fluvoxamine (b) t= .199, df =28 ,p= 0.84. Student's paired t-test of mean AUC of ACTH pre vs post fluvoxamine treatment fot the abused and not abused subjects (c) t= .-3.80, df =16 ,p= 0..002 and (d) t= .1.61, df =12 ,p= 0.134 respectively

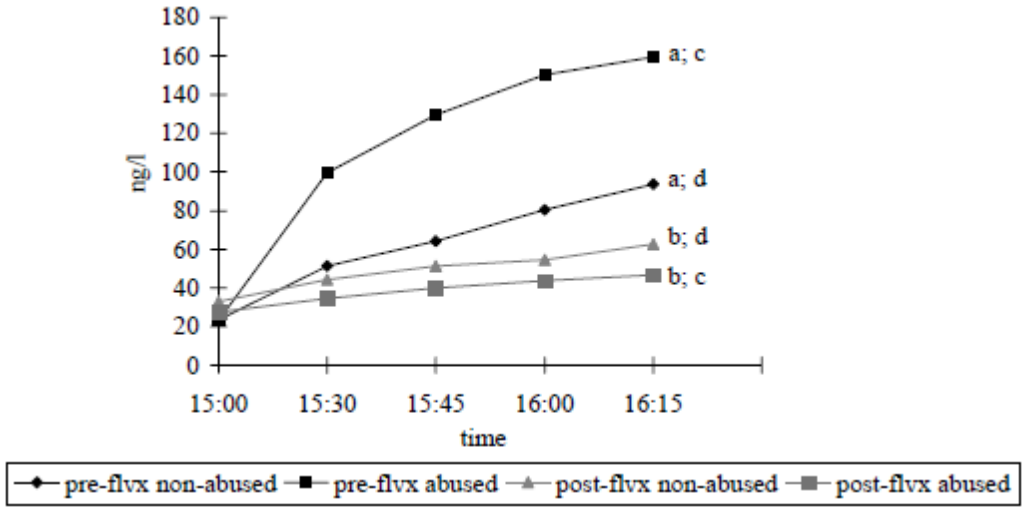


Fig 3.2(b) Concentration time curve of cortisol responses to DEX/CRH challenge pre and post fiuvoxamine treatment for abused (n =17) and not abused (n=13) BPD subjects. Student's t-test for independent samples of mean AUCs of ACTH of the abused subjects pre-fluvoxamine treatment (a) t = 1.69, df =27.93 ,p= 0.10 and post fluvoxamine (b) t = 0.352, df =16.93 ,p= 0.73. Student's paired t-test of mean AUC of ACTH 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= 0.106 respectively

3.3 Time Frame of the Fluvoxamine Effect on the HPA Axis:

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) after 6 weeks of fluvoxamine treatment (n=14) and after 12 weeks of fluvoxamine treatment (n=16),

respectively. As a result of the equal decrease in both groups no statistically significant group by time effect could be found (F (1.28) = 0.007, p=0.933), indicating that fluvoxamine is most likely to exert its effect in the first 6 weeks of treatment.

4. DISCUSSION

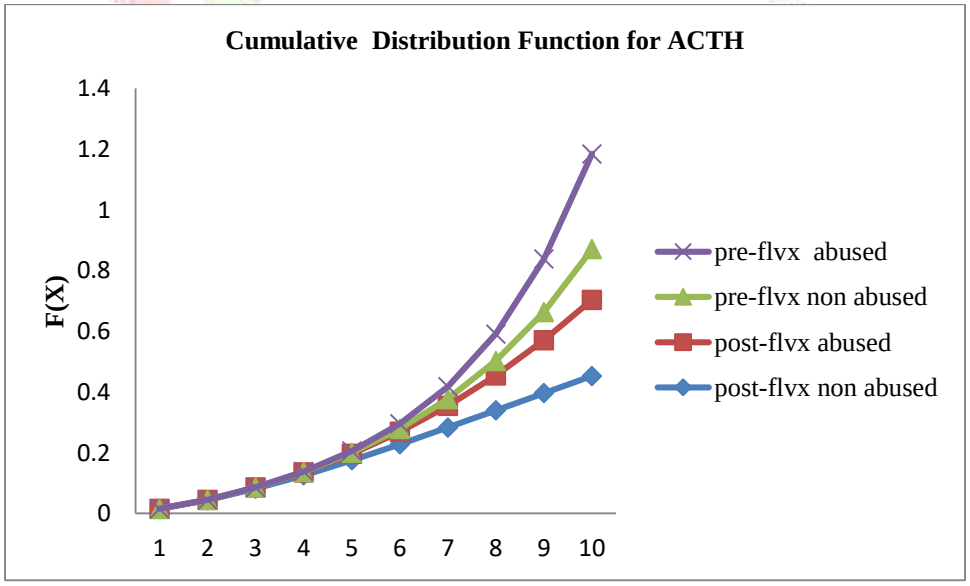
Fluvoxamine treatment was associated with a significant and robust reduction of the ACTH and cortisol response to the combined DEX/CRX challenge test in chronically abused BPD subjects. BPD subjects with no or incidental childhood abuse had low pre and post- treatment ACTH and cortisol responses to DEX/CRX challenge. The presence of a comorbid diagnosis of MDD or PTSD did not influence the effect of fluvoxamine on ACTH and cortisol response to the DEX/CRH test in these BPD subjects. The comparision of the 6 and 12 weeks treatment with fluvoxamine suggest that the decrease of the ACTH and cortisol response is already established in the first 6 weeks of the treatment. The robust decrease of the ACTH and cortisol response to DEX/CRH test after fluvoxamine treatment in the chronically childhood abused BPD subjects may reflect a reduction of the enhanced CRH/AVP drive in these subjects. (Rinne et al, 2002).

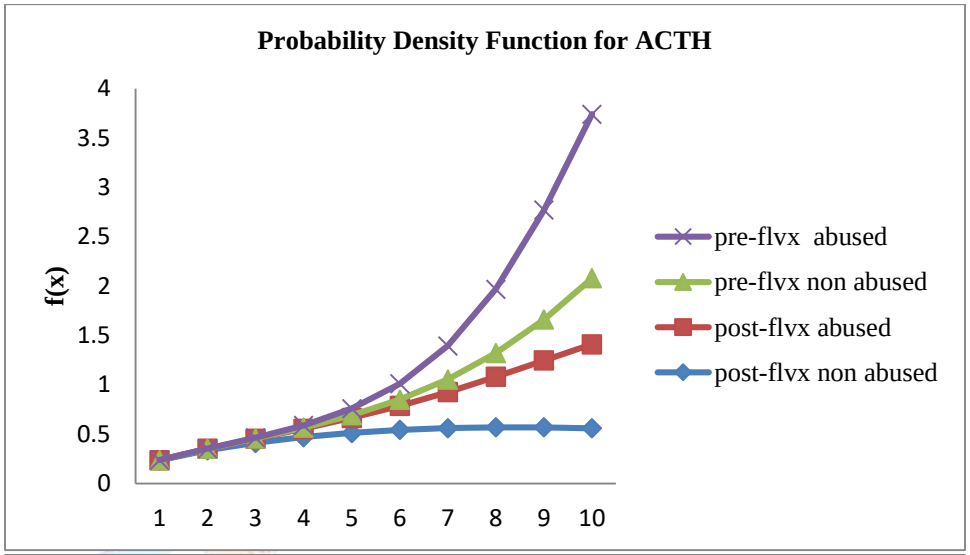
Preclinical research has provided some clues as to how to these effects of childhood abuse and fluvoxamine on the HPA axis evolve **[9].** It appeared that early life stressors such as maternal deprivation persistently enhance the responsiveness of the HPA axis in adulthood. The effect exerted by maternal deprivation resulted in the altered expression of the hippocampal mineralo (MR) and gluco-corticoid receptor (GR) sites in a manner that would explain the enhanced HPA responsiveness **[5].** In other studies, early stress was found to induce an increase in the number of hypothalamic CRH neurons and an increase in CRH and AVP m-RNA expression **[4].**

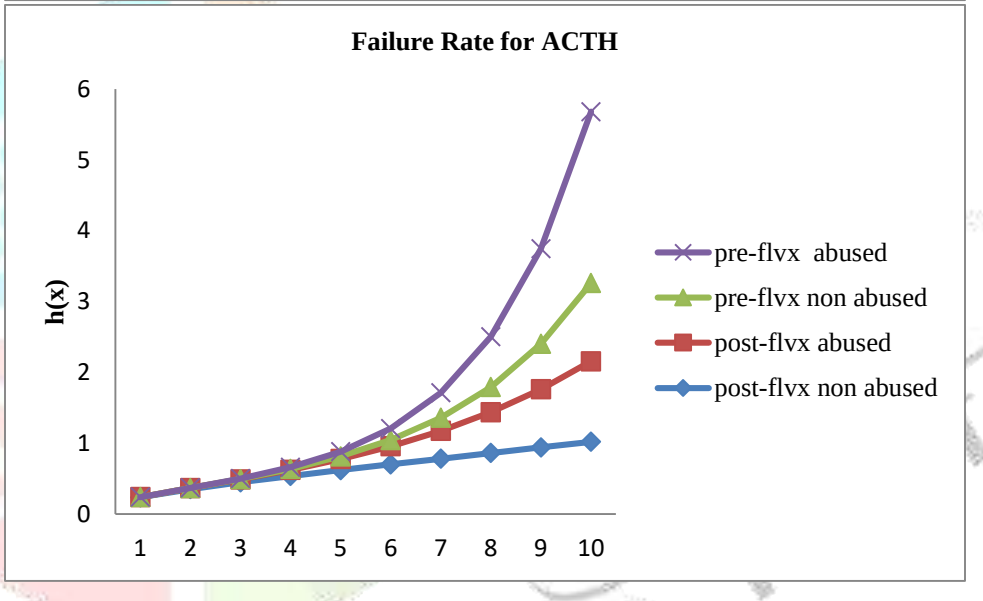
An elevated AVP/CRH release is likely to enhance the expression of pro-opiomelanocortin (POMC) synthesis and the release of its peptide product ACTH in pituitary corticotrophs. Preclinical studies on the effects of the chronic administration of different antidepressants demonstrate that a decrease of the HPA-axis activity is a final common pathway of antidepressant effects, but that the different antidepressants unfold their specific pharmacological efficacy on varying HPA-axis levels and receptor subsystems. Tricyclic antidepressants as well as the SSRI fluoxetine are likely to increase either GR m-RNA or MR m-RNA expression in the hippocampus, depending on the type of drug . Owing to the increase of hippocampal MRs and GRs, they are thought to regain their balance re-establishing the inhibitory tone on the PVN in the hypothalamus.

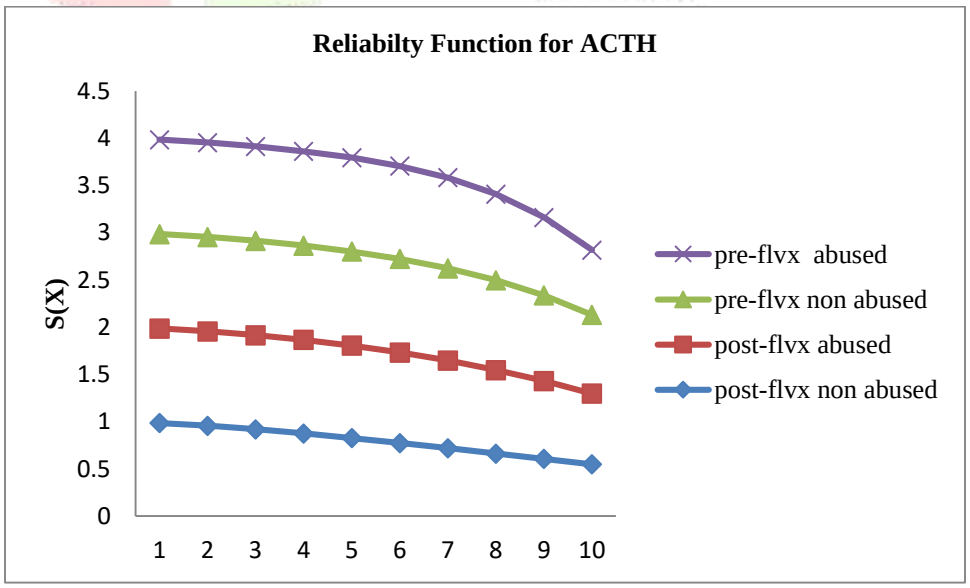
In accordance with this assumption, CRH m-RNA in the hypothalamic PVN and CSF CRH as week as AVP turn out to be decreased after fluoxetine treatment. In this paper, another (hypothetical) pathway of SSRI's action on the HPA axis may be of interest .The CRH neurons of the PVN and the locus coruleus (LC) maintain a positive feedback loop in case of stress **[8]** Sustained SSRI treatment leads to a reduced firing rate of noradrenergic neurons of the LC **[12].** Which is expected to have its repercussion on the hypothalamic CRH neurons and thus on the release of ACTH secretagogs.

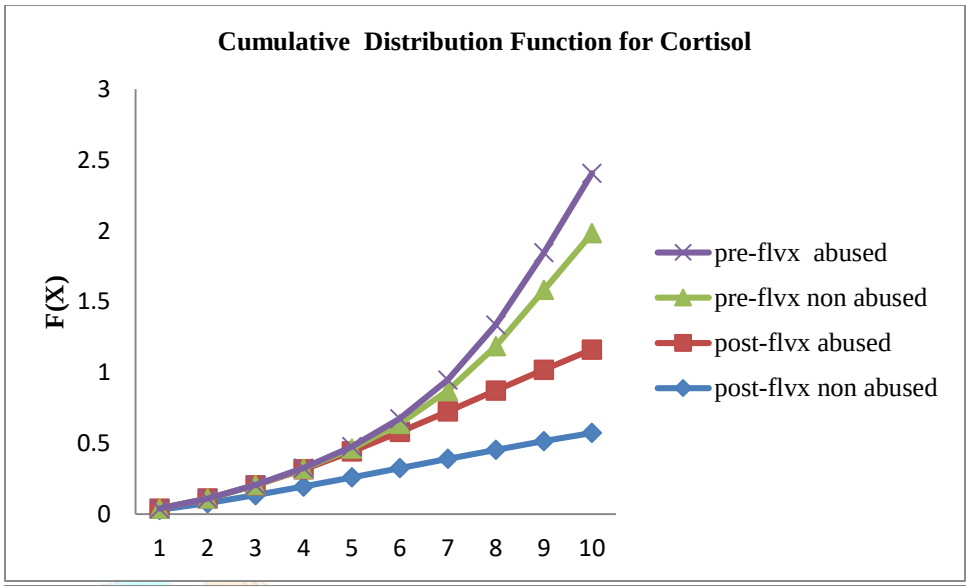
5. MATHEMATICAL RESULTS

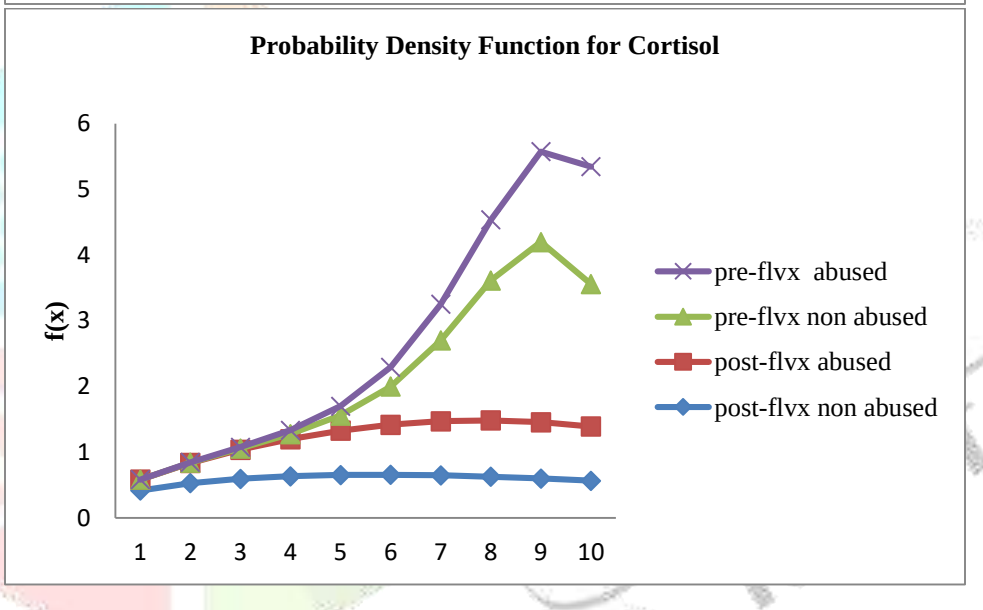


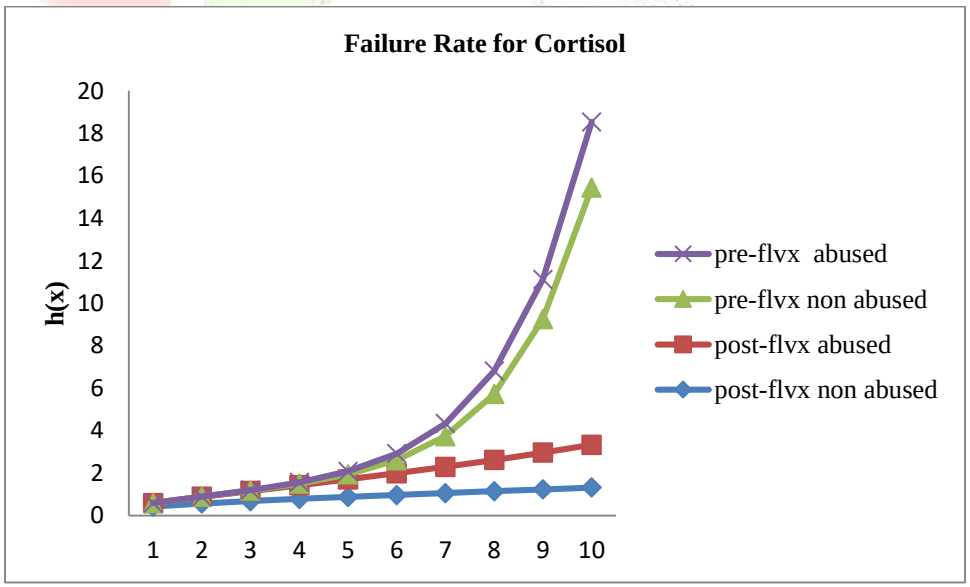

Probability Density Function for ACTH
f(x)
4
3.5
3
2.5
2
1.5
1
0.5
0
1 2 3 4 5 6 7 8 9 10
pre-flvx abused
pre-flvx non abused
post-flvx abused
post-flvx non abused

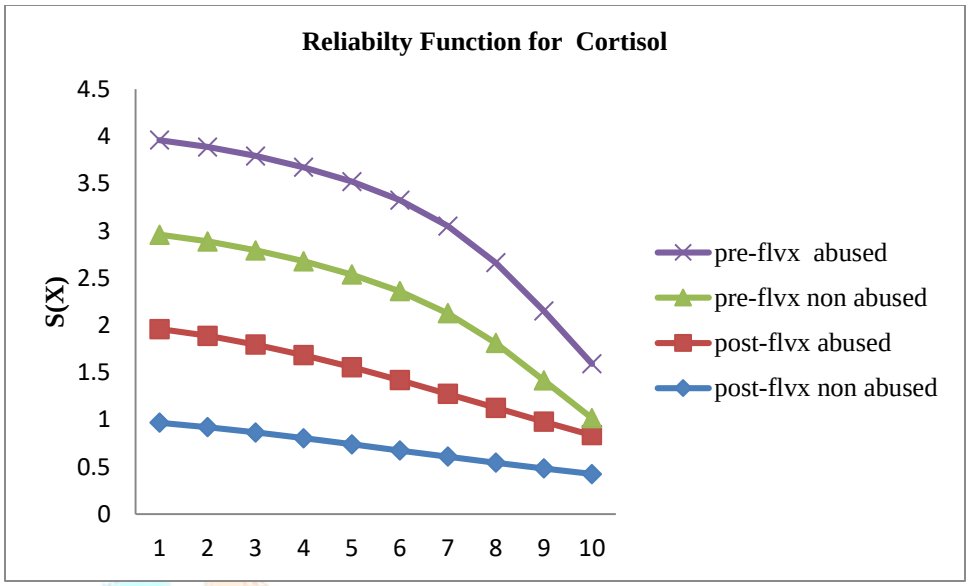

Failure Rate for ACTH
h(x)
6
5
4
3
2
1
0
1 2 3 4 5 6 7 8 9 10
pre-flvx abused
pre-flvx non abused
post-flvx abused
post-flvx non abused


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:

A three parameter Weibull exponential distribution has been successfully defined. A mathematical property of proposed model was rigorously discussed and it can be said that Weibull exponential distribution is more flexible than the exponential distribution. We have plotted cumulative distribution function, probability density function, Failure rate and reliability function of proposed model for ACTH and cortisol hormones. Using these mathematical reports we found that the BPD patients with a history of sustained childhood abuse showed the strongest reduction in ACTH and cortisol and fluvoxamine treatment reduces the hyper responsiveness of the HPA axis. Finally we conclude that reliability function of proposed model is well fitted with application part and conclusion is compared with medical report. This paper will be very useful in the field of insurance, engineering and medicine, economics and finance.

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