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A Mathematical 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:

It is possible to build up different software reliability models such as exponentiated Gumbel model, Dhillon model, exponentiated logistic model, Gumbel model and exponentiated log-logistic model. Here we have used exponential Gumbel model and Dhillion model for a psycho neuroendocrinological model. Which are described in section-3 and the corresponding results are obtained in section-5. Finally we have concluded in section-6.

Keywords: ACTH, Software Reliability models, probability density function.
Mathematical subject classification: $62H_{xx}$; $62NO_5$; $90B25$.

1. INTRODUCTION

New classes of reliability models have been proposed based on modifications of the existing model. Several exponentiated models have been studied quite extensively, since the work of **[1]** on exponentiated Weibull model due to the existence of simple elegant closed form solutions to many life testing problems. It can easily be justified under the assumption of constant failure rate but in the real world, the failure rates are not always constant. Hence, indiscriminate use of exponentiated lifetime model seems to be inappropriate and unrealistic. A classical generalization of the exponentiated family is known as Weibull family. Weibull model **[5]** is one of the most commonly used lifetime distributions in reliability and lifetime data analysis. It is flexible in modeling failure time data, as the corresponding hazard rate function can be increasing, constant or decreasing. But in many applications in reliability and survival analysis, the hazard rate function can be of bathtub shape. The hazard rate function

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plays a central rule to the work of reliability engineers, **[4]** and **[6]** and references therein. Models with a bathtub hazard rate function are needed in reliability analysis and decision making when the life time of the system is to be modeled.

2. MATHEMATICAL MODELS

2.1 .EXPONENTIATED GUMBEL MODEL

The Exponentiated Gumbel model has been proposed as a generalization of the classical Gumbel model **[8]**. Since the Gumbel model yields narrower confidence intervals than the some other extreme value models but has also the risk of under estimating the return level. Hence the choice of model is not insignificant.

Recently a generalization of the Gumbel model also called as Exponentiated Gumbel model was introduced by **[9].** The cumulative distribution function of Exponentiated Gumbel model with two parameters is given by

$$F(X) = \exp\{-\alpha\, exp\ [-(x \div \sigma)]\} : -\infty < x < \infty, \alpha > 0, \rho > 0$$

Where

$\alpha > 0$ *is the shape and* $, \rho > 0$ *is the scale parameter.*

The probability density function is given by

$$f(x) = \frac{\alpha}{\sigma} \exp\left\{-\left[\frac{x}{\sigma}\right]\right\} exp\ \left(-\alpha \exp\left\{-\left[\frac{x}{\sigma}\right]\right\}\right) : -\infty < x < \infty, \alpha > 0, \rho > 0$$

The two parameter Exponentiated Gumbel model will be denoted by EG (α, ρ)

2.2 DHILLON MODEL

A new reliability model with two parameters which is flexible like the weibull model and with the capacity to also describe a U-shaped hazard function is described in **[5].** This model is revisited by **[4]** and shown that it has an inverted U- shaped similar to the log-logistic hazard function, but with a different curvature, especially after the peak. For $\alpha > 0, \beta > 0$ the two parameter and Dhillon model has the distribution function is given by

$$f(x) = 1 - exp\left\{-[\log(\alpha x + 1)]^{\beta+1}\right\}; x \geq 0, \alpha > 0, \beta > 0$$

Where

$\alpha > 0$ *is the shape and* $, \beta > 0$ *is the scale parameter.*

The probability density function is given by

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$$f\ (x) = \frac{\alpha(\beta+1)}{\sigma\ x+1}\ [\log(\alpha x+1)]^{\beta}\ exp\left\{-\ [\log(\alpha x+1)]^{\beta+1}\right\}; x\ \geq 0\ , \alpha > 0, \beta > 0$$

The two parameter Dhillon model will be denoted by DL $(\alpha, \beta\ )$

3. APPLICATION

3.1(a) 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).

3.1(b) 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 3.1 (c)). 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

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D=87.0) to 20.2 (SD=59.1) (F (1.28) = 4.08, p=0.058; see also Figure 3.1(d)).

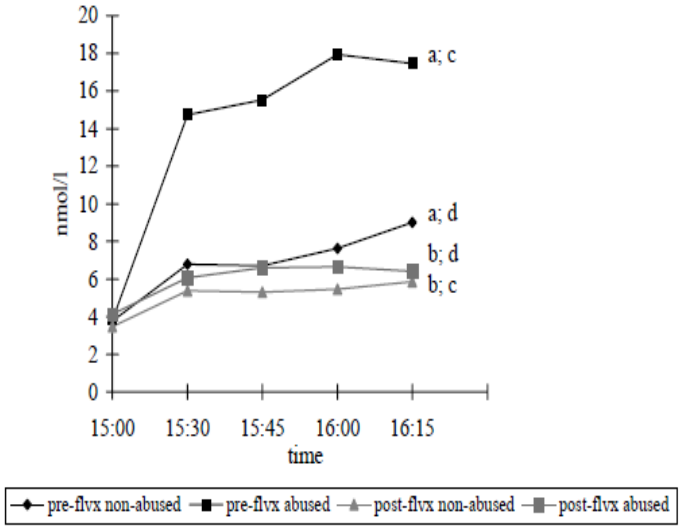

Fig 3.1(c) Concentration time curve of ACTH responses to DEX/CRH challenge pre and post fiuvoxamine treatment for abused (n =17) and not abused (n=13) BPD subjects. Student's t-test for independent samples of mean AUCs of ACTH of the abused subjects pre-fluvoxamine treatment (a) t= 3.390, df =28 ,p= 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

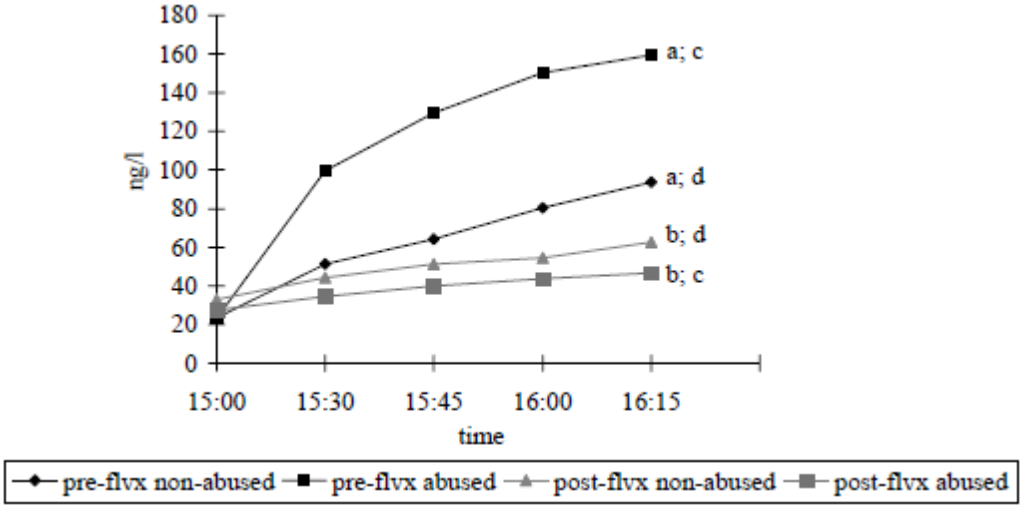

Fig 3.1(d) Concentration time curve of cortisol responses to DEX/CRH challenge pre and post fiuvoxamine treatment for abused (n =17) and not abused (n=13) BPD subjects. Student's t-test for independent samples of mean AUCs of ACTH of the abused subjects pre-fluvoxamine treatment (a) t = 1.69, df =27.93 ,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

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3.1 (e) 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 **[2].** 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 **[3].** 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. 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

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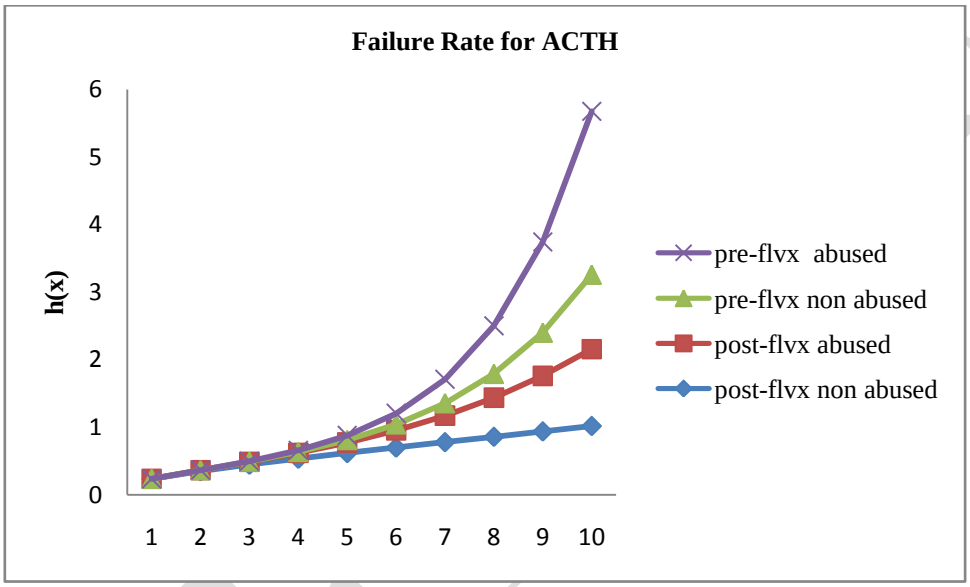
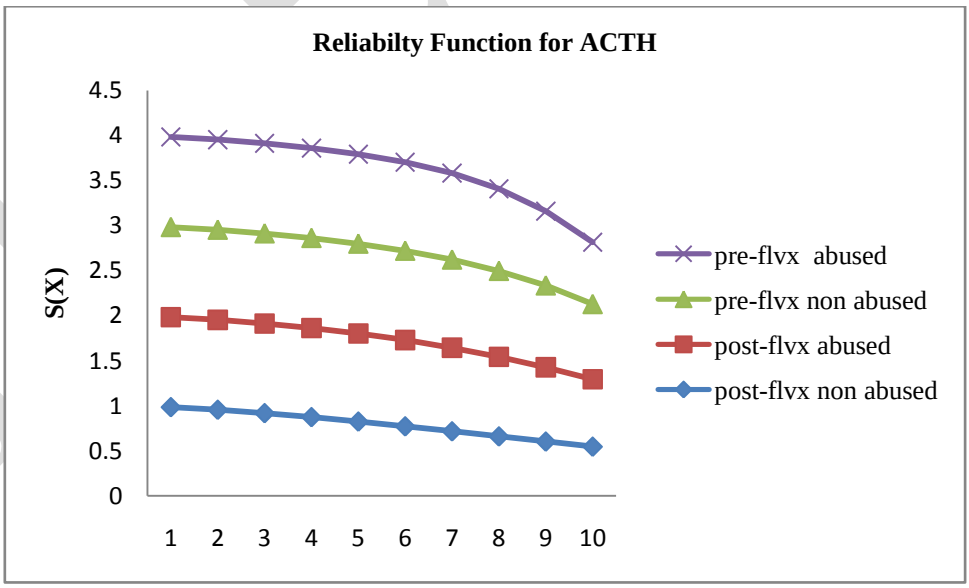
in the hypothalamus. In accordance with this assumption, CRH m-RNA in the hypothalamic PVN and CSF CRH as week as AVP turn out to be decreased after fluoxetine treatment. In this paper, another (hypothetical) pathway of SSRI's action on the HPA axis may be of interest .The CRH neurons of the PVN and the locus coruleus (LC) maintain a positive feedback loop in case of stress Sustained SSRI treatment leads to a reduced firing rate of noradrenergic neurons of the LC **[7].** Which is expected to have its repercussion on the hypothalamic CRH neurons and thus on the release of ACTH secretagogs.

5. MATHEMATICAL RESULTS





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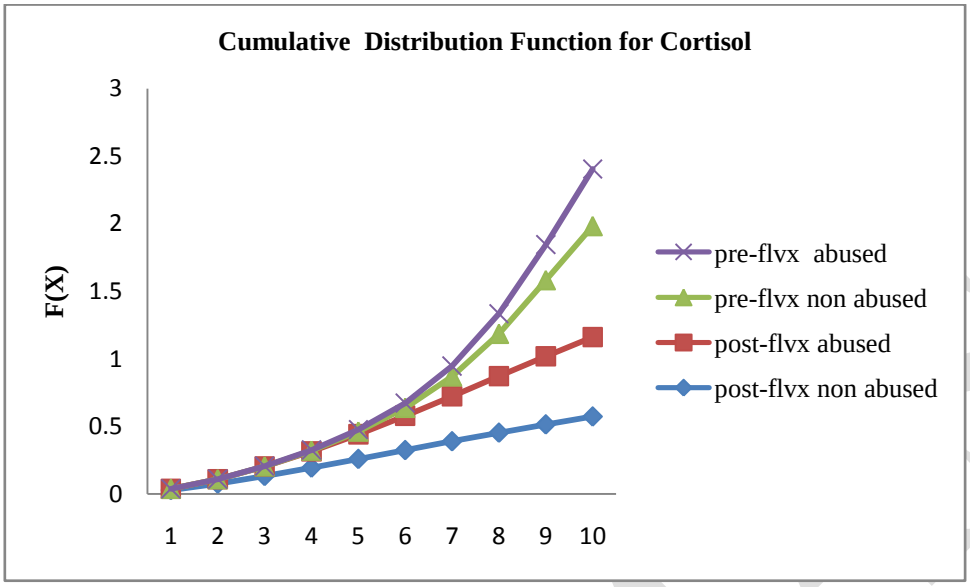

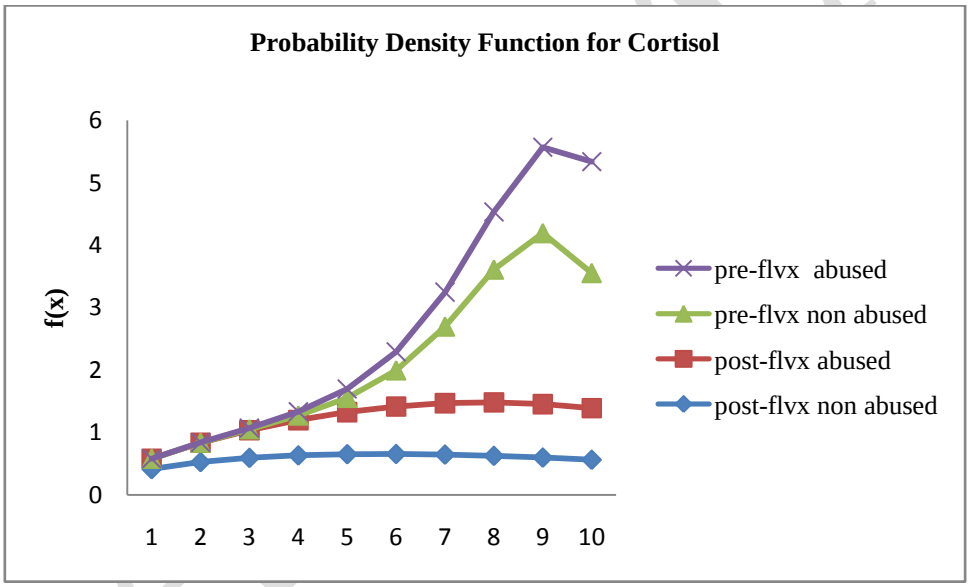

6. CONCLUSION

By using Gumbel's exponential distribution and Dhillon's model the Probability density function and Cumulative distributive function have been obtained. Figures in section 5 shows that, when the time is increased the conditional probabilities for secretion of 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

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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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