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A Mathematical Model for the Activation of the Hypothalamic – Pituitary – Adrenal Axis in Generalized Anxiety and Panic by Plasma Cortisol and Prolactin Levels using Four Parameters Transmuted Additive Weibull Distribution

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Abstract:

The Weibull distribution has been used in many different fields with many applications. Researchers have been developing various extensions and modified forms of the Weibull distribution, with different number of parameters. In this paper the Transmuted Additive Weibull distribution is used to find out the hazard rate function for the activation of the hypothalamic – pituitary – adrenal axis in generalized anxiety and panic by the plasma cortisol and prolactin. The medical part focuses on the differential activation of the hypothalamic – pituitary – adrenal (HPA) axis in generalized anxiety and panic. In this paper, the idea of finite state continuous time markov chain is also used to find out the internal states between the states P (before the speech performance) and F (end of the speech) for the Simulated Public Speaking (SPS) test of the medical part. The hazard rate functions for these two internal states are also find out and compared with the whole time practical session.

Keywords: Transmuted Additive Weibull Distribution, Reliability Function, Finite State Continuous Time, General Adaptation Syndrome, Anxiety, Panic.

Mathematical Subject Classification: 60 Gxx

1. Mathematical Model

Introduction

A random variable X is said to have a additive weibull distribution function (cdf) is

$$F(x) = 1 - e^{-\alpha x^{\theta} - \gamma x^{\beta}}, x \geq 0 \quad \ldots\ldots (1)$$

where α, θ, γ and β are non – negative, with $\theta < 1 < \beta$ $(or\ \beta < 1 < \theta)$. Note that θ and β are the shape parameters and α and γ are the scale parameters.

The probability density function (pdf) of the additive Weibull distribution is

$$f(x) = \left(\alpha\theta x^{\theta-1} + \gamma\beta x^{\beta-1}\right)e^{-\alpha x^{\theta} - \gamma x^{\beta}} \quad \ldots\ldots (2)$$

and the hazard rate function is given by

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

$$= \frac{\left(\alpha\theta x^{\theta-1} + \gamma\beta x^{\beta-1}\right)e^{-\alpha x^{\theta} - \gamma x^{\beta}}}{e^{-\alpha x^{\theta} - \gamma x^{\beta}}}$$

$$= \left(\alpha\theta x^{\theta-1} + \gamma\beta x^{\beta-1}\right)$$

The change point x where the hazard rate function h(x) achieves its minimum is at

$$x = \left(\frac{\theta(1-\theta)\alpha}{\beta(\beta-1)\gamma}\right)^{\frac{1}{\beta-\theta}}$$

when $\theta < 1 < \beta$. It is important to note that the change point remains the same when $\beta < 1 < \theta$. In this paper the four parameter additive Weibull distribution is embedded in a larger family obtained by introducing an additional parameter. The generalized distribution is called as the Transmuted Additive Weibull Distribution.

1.1 Transmuted Additive Weibull Distribution

A random variable X is said to have a Transmuted probability distribution with cdf F(x), if

$$F(x) = (1 + \lambda)G(x) - \lambda G(x)^2, |\lambda| \leq 1$$

where G(x) is the cdf of the base distribution. Observe that at λ = 0 we have the distribution of the base random variable. Aryal and Tsokos [1] studied the Transmuted Weibull as a generalization of Weibull distribution. Khan and King [5] extended the Modified Weibull to a Transmuted Modified Weibull distribution [7]. Now using (1) and (2) we have the cdf of the Transmuted Additive Weibull Distribution

$$F_{TAW}(x) = \left(1 - e^{-\alpha x^{\theta} - \gamma x^{\beta}}\right)\left(1 + \lambda e^{-\alpha x^{\theta} - \gamma x^{\beta}}\right) \quad \ldots\ldots (3)$$

where θ and β are the shape parameters representing the different patterns of the Transmuted Additive Weibull Distribution and are positive, α and γ are the scale parameters representing the characteristic life and are also positive, and λ is the transmuted parameter. The probability density function (pdf) of a Transmuted

Additive Weibull Distribution is given by

$$f_{TAW}(x) = \left(\alpha\theta x^{\theta-1} + \gamma\beta x^{\beta-1}\right)e^{-\alpha x^{\theta}-\gamma x^{\beta}}\left(1-\lambda+2\lambda e^{-\alpha x^{\theta}-\gamma x^{\beta}}\right) \quad \ldots\ldots (4)$$

The Transmuted Additive Weibull Distribution is a very flexible model that approaches to different distributions when its parameters vary.

Because of the analytical structure of the Transmuted Additive Weibull distribution, it can be a useful model to characterize failure time of a system. The reliability function also known as survival function of the Transmuted Additive Weibull distribution is denoted by $R_{TAW}(t)$ and is given as

$$R_{TAW}(t) = 1 - F_{TAW}(t)$$
$$= 1 - \left(1 - e^{-\alpha t^{\theta}-\gamma t^{\beta}}\right)\left[1 + \lambda e^{-\alpha t^{\theta}-\gamma t^{\beta}}\right]$$
$$= e^{-\alpha t^{\theta}-\gamma t^{\beta}}\left(1-\lambda+\lambda e^{-\alpha t^{\theta}-\gamma t^{\beta}}\right) \quad \ldots\ldots (5)$$

One of the most important quantities characterizing life phenomenon in life testing analysis is the hazard rate function defined by

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

The hazard rate function for a Transmuted Additive Weibull distribution is given by

$$h_{TAW}(t) = \frac{\left(\alpha\theta t^{\theta-1} + \gamma\beta t^{\beta-1}\right)\left(1-\lambda+\lambda e^{-\alpha t^{\theta}-\gamma t^{\beta}}\right)}{\left(1-\lambda+\lambda e^{-\alpha t^{\theta}-\gamma t^{\beta}}\right)} \quad \ldots\ldots (6)$$

It is important to note that the unit for $h_{TAW}(t)$ is the probability of failure per unit of time, distance or cycles. The failure rates for several different distribution can be obtained by simply changing the parameters [12].

The cumulative hazard function, which describes how the risk of a particular outcome changes with time, is given by

$$H_{TAW}(t) = \int_0^t h_{TAW}(x)dx$$
$$= -log\left[e^{-\alpha t^{\theta}-\gamma t^{\beta}}\left(1-\lambda+\lambda e^{-\alpha t^{\theta}-\gamma t^{\beta}}\right)\right]$$
$$H_{TAW}(t) = \alpha t^{\theta} + \gamma t^{\beta} - log\left(1-\lambda+\lambda e^{-\alpha t^{\theta}-\gamma t^{\beta}}\right)$$

Notice that the unit for $H_{TAW}(t)$ is the cumulative probability of failure per unit of time, distance or cycles. It describes how the risk of a particular outcome changes with time for a Transmuted Additive Weibull Distribution.

The hazard rates of some sub-models of the transmuted additive Weibull distribution are given below:

I. Hazard rate of Transmuted Modified Weibull Distribution

$$h_{TMWD}(t) = \frac{\left(\alpha + \gamma\beta t^{\beta-1}\right)\left(1-\lambda+\lambda e^{-\alpha t-\gamma t^{\beta}}\right)}{\left(1-\lambda+\lambda e^{-\alpha t-\gamma t^{\beta}}\right)}$$

II. Hazard rate of Additive Weibull Distribution

$h_{TMWD}(t) = \alpha\theta t^{\theta-1} + \gamma\beta t^{\beta-1}$

1.2 Finite State Continous Time Markov Chain

The general idea is to recognize a suitable regenerative structure, like what happens to a discrete time, discrete space markov chain each unit time it comes back to a point [4, 11]. Then decompose the path into blocks which are i.i.d. This idea can also be applied to continuous time, discrete space chains. In this paper, we discuss a continuous time, discrete space Markov Chain, with time homogeneous transition probabilities. Let S be the state space and suppose $(X_t, t \geq 0)$ is a process defined on $(\Omega, \mathcal{F}, \mathbb{P})$, with values in S which is finite [2, 3]. For each $t, \omega \to X_t(\omega)$ is a measusrable map from $(\Omega, \mathcal{F}) \to S$. Look at the path: $t \to X_t(\omega)$ for fixed ω. In the finite state space case, we expect this path to be almost surely a step function, with only a finite time – homogeneous Markov property if

- Conditionally given X_t, the process $(X_s, 0 \leq s \leq t)$ and $(X_u, t \leq u \leq \infty)$ are independent
- $(X_{t+v},\ v \geq 0 \mid X_t = i)$ is distributed like $(X_v,\ v \geq 0 \mid X_0 = i)$. Introduce the transition matrices $P_t = \| P_t(i,j) \|_{i,j}$, where
  $P_t(i,j) = P(X_{s+t} = j \mid X_s = i), s \geq 0, i, j \epsilon S$

The definition of P_t and the time – homogeneous Markov property yield:

- $P_t(i,j) \geq 0$
- $\sum_{j\epsilon S} P_t(i,j) = 1$
- The semi group property: (Chapman Kolmogorov equation) $P_s P_t = P_{s+t}$

Right - continuous paths make $X_t \to X_0, a.s\ as\ t \to 0^+$, which implies $\lim_{t\to 0^+} P_t = I$ (the identity matrix). Combining with the semigroup property, we know $\lim_{r\to t^+} P_r = \lim_{s\to 0^+} P_{t+s} = \lim_{s\to 0^+} P_s P_t = I P_t = P_t$

Thus P_t is a right continuous function of t. In fact, P_t is not only right continuous but also continuous and even differentiable. Accepting this, let $Q = \frac{d}{dt} P_t \mid t = 0$. The semi-group property easily implies the following backward and forward equations: $\frac{d}{dt} P_t = Q P_t = P_t Q$

Hence there is representation:

$$P_t = \exp(Qt) = I + Qt + \frac{Q^2 t^2}{2!} + \cdots$$

In particular,

$P_t(i,j) = 1_{(i=j)} + Q(i,j)t + o(t) as\ t \to 0^+$

Note that $P_t(i,j) \geq 0$, so $Q(i,j) \geq 0\ for\ j \neq i$

And $\sum_{j\epsilon S} P_t(i,j) = 1$ implies $\sum_{j\epsilon S} Q(i,j) = 0$

Let, $q_i := -Q(i,i) = \sum_{j\neq i} Q(i,j) \geq 0$.

Let J_r denote time of the r^{th} jump. By the Markov property, J_1 has the memoryless property $\mathbb{P}_i(J_1 > s + t \mid J_1 > s) = P_i(P_i > t)$

Notice $\frac{d}{dt}\mathbb{P}_i(J_i > t)\,|_{t=0} = \frac{P_i(t<J_1\leq t+dt)}{dt}\,|_{t=0}$

$= \sum_{j\neq i}\frac{P_i(X_{t=i},X_{t+dt=j})}{dt}\,|_{t=0}$

$= \sum_{j\neq i}P_t(i,i)\frac{P_{dt}(i,j)}{dt}\,|_{t=0}$

$= \sum_{j\neq i}Q(i,j)$

$= -q_i$

Hence $\mathbb{P}_i(J_i > t)\,|_{t=0} = e^{-q_i t}\ (t \geq 0)$

That is the P_i distribution of J_1 is exponential (q_i). Note that $q_i=0$ means i is absorbing: $P_t(i,i) = 1$ for all t.

Now assume $q_i > 0$. Let $\hat{p}(i,j) := \begin{cases} Q(i,j)/q_i & ,j\neq i \\ 0 & otherwise \end{cases}$

Then, $\sum_{j\neq i}\hat{p}(i,j) = 1$

So $\hat{p}$ is a transition probability matrix. From the exponential (q_i) distribution of J_1,

$\mathbb{P}_i(X\ first\ leaves\ i\ in\ (t,t+dt)\mid X_s = i, 0\leq s\leq t) = q_i dt$

Hence, for $j \neq i$

$\mathbb{P}_i(X\ jumps\ to\ t\ in\ (t,t+dt)\mid X_s = i, 0\leq s\leq t) = P_i(X_{J_1} = j)q_i dt$

On the other hand

$\mathbb{P}_i(X\ jumps\ to\ t\ in\ (t,t+dt)\mid X_s = i, 0\leq s\leq t) = P_{dt}(i,j) = Q(i,j)q_i dt$

Comparing the last two facts

$$\mathbb{P}_i(X_{J_1} = j) = \frac{Q(i,j)}{q_i}\ \ for\ j\neq i$$

Set $J_0 = 0$, similar arguments enable us to get for r = 0, 1, 2, ……

$P(X_{J_{r+1}} = j \mid X_{J_r} = i) = \hat{p}(i,j)$

Starting from I, $(X_0, X_{J_1}, X_{J_2}, \ldots\ldots)$ is a discrete Markov chain with transition matrix $\hat{p}$, which is called the embedded jump chain. Moreover, conditionally given $X_0 = i_0$, $X_{J_1} = i_1$, $X_{J_2} = i_2, \ldots\ldots\ldots$, the holding times $J_1, J_2 - J_1, J_3 - J_2, \ldots\ldots$ are independent exponential variables with parameters $q_{i_0}, q_{i_1}, q_{i_2}, \ldots\ldots$ And given any matrix Q with non – negative off – diagonal elements and row sums identically zero, we can construct a Markov chain with semigroup $P_t = \exp(Qt)$ as such a hold – jump process. Say, the chain starts from i_0, it says at i_0 for a period of time with exponential (q_{i_0}) distribution. Then it jumps to another point i_1 with probability $\hat{p}(i_0,i_1)$. And stays at i_1 for a period of time with exponential (q_{i_1}) distribution, then jumps to i_2 with probability $\hat{p}(i_1,i_2)$. And so on. Provided Q is bounded or not too badly unbounded, this construction also makes sense for infinite S.

2. APPLICATION

2.1 Introduction

The concept of stress is based on the observation that different kinds of physical or psychological demands on the organism elicit the same set of bodily changes, the so called General Adaptation Syndrome (GAS). The most characteristic stress response is the release of adrenocorticotropic hormone (ACTH) and corticoids (cortisol in humans) into the blood stream as a result of activation of the hypothalamic – pituitary

– adrenal (HPA) axis. In addition to the HPA axis, acute stress also activates the sympathetic division of the neurovegetative nervous system as part of the fight / flight reaction or emergency response. As a result, noradrenaline is released from peripheral sympathetic nerve fibers in different tissues, and adrenaline from the adrenal medulla into the blood stream.

To test the GAS hypothesis, the following five stressors are to be used: immobilization, hemorrhage, cold exposure, pain, or hypoglycemia. With the exception of immobilization stress, these stressors also differed in their intensities. Their results showed marked heterogeneity of neuroendocrine responses to various stressors and that each stressor has a neurochemical "signature". By examining changes of Fos immunoreactivity in various brain regions upon exposure to different stressors, they also described stressor – specific adaptive compensatory responses. This view may help to understand the seeming paradox on panic attacks and the HPA axis that is discussed as follows.

Anxiety, fear and panic are emotions related to threat. Anxiety is the emotion related to risk – assessment behavior that is evoked in situations when the danger is uncertain (potential threat); either because the context is novel or because the danger stimulus (e.g. a predator) had been present in the past, but is no longer in the environment. In contrast, fear is related to defensive strategies that occur in response to actual danger that is at a certain distance from the prey (distal threat). Finally, panic corresponds to the vigorous flight reaction evoked by very close danger (proximal threat), such as an approaching predator or by acute cutaneous pain. Complete immobility also occurs in response to proximal danger, as well as defensive fight, which occurs when flight is impossible. Concerning psychopathology, it has been suggested that the same neurobiological processes that regulate anticipatory anxiety are involved in generalized anxiety disorder (GAD); the ones that control fear, in phobic disorders, and those organizing proximal defense, in panic danger (PD) [8].

2.2 Neuroendocrinology of panic and anxiety:

A naturally occurring PA can be considered as a traumatic stressor. Assuming the GAS hypothesis – there is single stereotyped hormonal response to all kinds of stressors, it is expected that the HPA axis would be much more activated by a panic attack than by anxiety. Yet, the majority of the reported results indicate that the HPA axis is little affected by PAs. Thus, a review of the literature on stress hormone responses during Pas showed that real – life PAs as well as those induced by selective panicogenic agents, such as lactate and carbon dioxide, do not activate the HPA axis.

The main psychological procedures for inducing experimental anxiety in human beings for pharmacological studies have been the aversive conditioning of the skin conductance response and the Simulated Public Speaking (SPS) tests. While the drug profile for the former is similar to that of GAD, SPS has a pharmacological profile that resembles PD and social anxiety disorder, and is believed to mobilize the same neural network that is involved in these disorders. Two studies have been conducted to investigate whether SPS would affect HPA axis functioning.

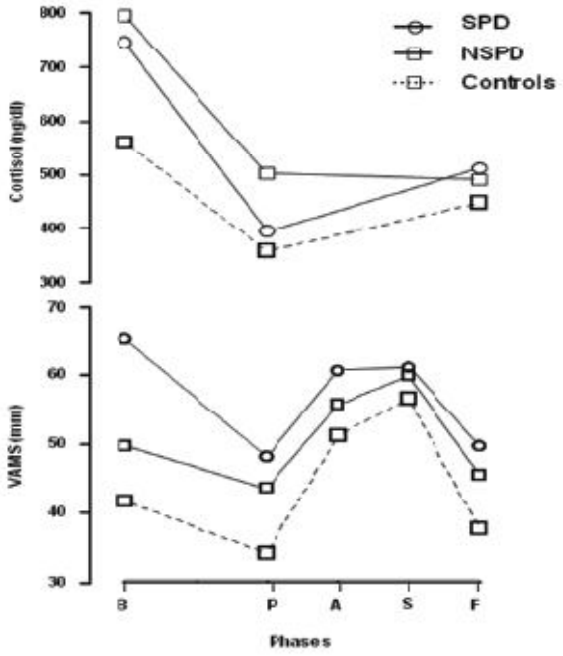

Figure 2.2.1

Upper Panel: Mean Salivary Cortisol concentration before and after the simulated public speaking (SPS) test measured in 18 symptomatic panic patients, 16 nonsymptomatic patients and 17 healthy controls. The initial measure was taken 25 minutes after the subject arrived in the laboratory. The last measure is the average of the highest value for each participant along 60 minutes starting at end of the speech. Measurements were taken immediately, 15, 30 and 60 minutes after the speech.

Lower Panel: Mean VAMS anxiety factor along the experimental session in the same subjects. Session phases are: B – Initial, P – pre test, A – Speech preparation, S – Speech performance, F – Final.

In the SPS test, each participant is requested to prepare a speech and talk in front of a video camera, the performance being recorded on videotape. Anxiety and other subjective states are evaluated by a psychometric instrument, the Visual Analog Mood Scale (VAMS). Also, bodily symptoms related to anxiety are assessed by the Bodily Symptom Scale (BSS). In the first endocrinological study the participants were divided into three groups: 18 symptomatic panic patients, 16 nonsymptomatic, drug – treated panic patients, and 17 healthy controls. Along the experimental session, the VAMS anxiety index and the total score of the BSS were higher in symptomatic patients than in controls, nonsymptomatic patients lying in between. In every group, the level of salivary cortisol was high at the beginning of the experimental session, and decreased after 70 minutes. This fall parallels the decrease in the VAMS anxiety factor and in BSS ratings, and appears to reflect habituation of the initial, anticipatory anxiety evoked by exposure to the new and potentially threatening laboratory environment. Accordingly, there has been a positive correlation between the initial

level of cortisol and VAMS anxiety index and BSS scores to the initial levels, but failed to increase salivary cortisol measured along 60 minutes, starting at the end of the speech (Figure 2.2.1). Therefore, SPS do not seem to activate the HPA axis, in contrast to anticipatory anxiety.

The second study was aimed at evaluating the effects of escitalopram, a very potent and selective 5 – HT reuptake inhibitor, on SPS. Healthy male volunteers received, in a double – blind randomized design, placebo (n=12), 10(n=17) or 20(n=14) mg of escitalopram, two hours before the test. Both doses of escitalopram did not affect the increase in VAMS anxiety scores determined by speech preparation or performance, but prolonged the rise induced by SPS. The most important results for this study are that the test itself did not significantly change cortisol plasma levels; neither did it change the levels of prolactin. Therefore, once more SPS failed to activate the HPA axis. However, under the highest dose of escitalopram, cortisol and prolactin increased immediately after the SPS. The last result suggest that 5 – HT modulates the release of stress hormones.

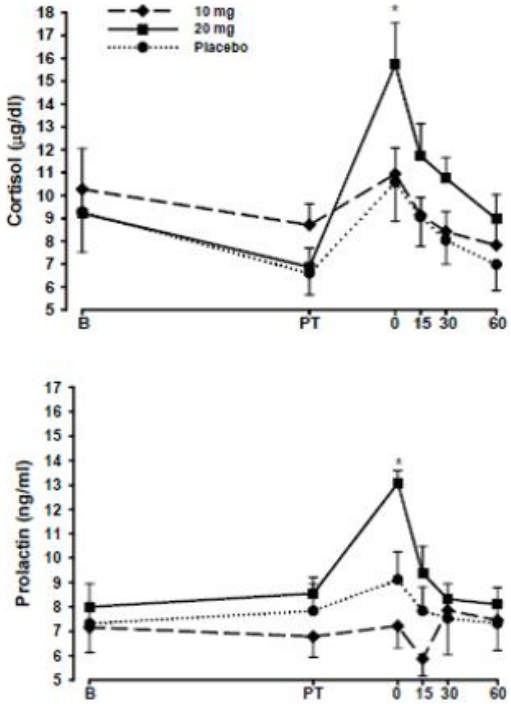

Figure 2.2.2

Plasma cortisol and prolactin levels along the SPS experimental session, measured in 37 healthy male volunteers treated with an acute oral doses of 10 mg (n=14) or 20 mg (n=11) of escitalopram, compared to placebo (n=12). Measurements were taken 60 minutes after the arrival in the laboratory (B), two hours after drug or placebo intake and before the speech (P), as well as immediately (0), (15), (30) and (60) minutes after the end of the speech. *Significantly different from PT and from the other two groups.

In contrast to the above SPS test, a similar procedure known as the Trier Social Stress Test (TSST), in which the participant faces an audience and is requested to perform arithmetical calculations [6], has been shown to increase salivary cortisol in normal volunteers, but fail to do so in PD patients. These results further support the view that PD patients lack cortisol responsivity to acute uncontrollable psychosocial stress. This unresponsiveness of the HPA axis seems to be rather specific, since in the mentioned study a normal cortisol awakening response in the morning has been recorded in the same patients.

The preceding evidence indicates that anxiety and panic are qualitatively different emotional states, which are related to the defense reactions to potential and proximal threat, respectively. Equally different are the related pathologies, GAD and PD, which differ both in their symptomatology and in the response to pharmacotherapy. Thus, specific neurobiological processes underlie each of these conditions. In regard to stress hormones, the analyzed data suggest that while anxiety activates both the HPA and the sympatho – adrenal axes, the panic attack causes major sympathetic activation, but has little effect on the HPA axis.

At a more general level, the distinction between the hormonal responses to anxiety as compared to panic supports the view held by Palkovits that there are specific adaptive responses to each types of stress. This casts doubts on the existence of GAS and, therefore on Selye's original concept of stress itself. Even the alternative concept of stress as "a state of threatened to homeostasis" [9] may be redundant to Cannon's notion of homeostasis, which implies that the organism tends to keep its internal state within narrow limits through specific adaptive responses that tend to connect any provoked imbalance.

Thus in the second study (Plasma cortisol and prolactin levels along the Simulated Public Speaking Test) there must be two internal states between the two existing states, i.e. before the speech performance (State P) and end of the speech (State F). For these two internal states the hazard rate functions are find out for the plasma cortisol and prolactin levels as in figures 3.3, 3.4, 3.5 & 3.6 and are compared with the whole time practical session.

3. Mathematical Results:

Mathematical representations for finding the hazard rate function of the Plasma cortisol and Prolactin levels by using equation (6) of Transmuted Additive Weibull Distribution for Figure 2.2.2.

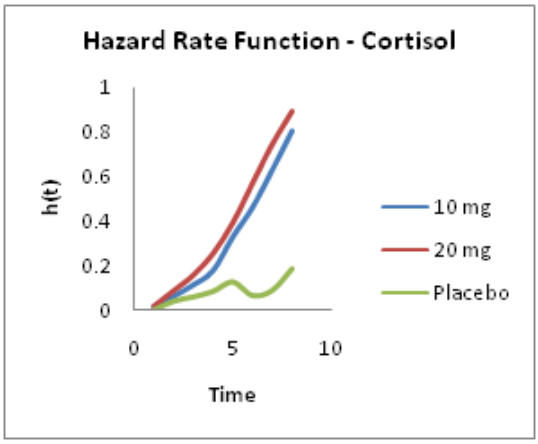

Figure 3.1

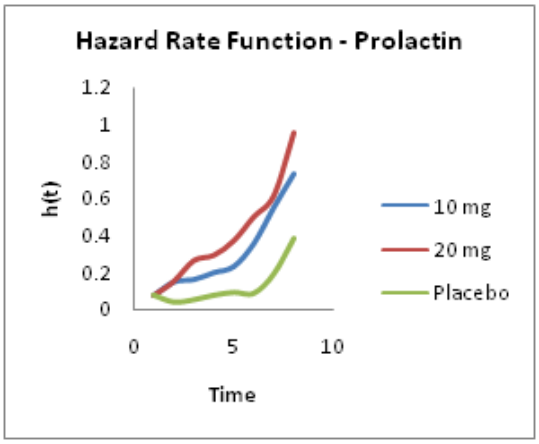

Figure 3.2

Hazard Rate Functions for the first internal state during the speech of Plasma cortisol and Prolactin Levels:

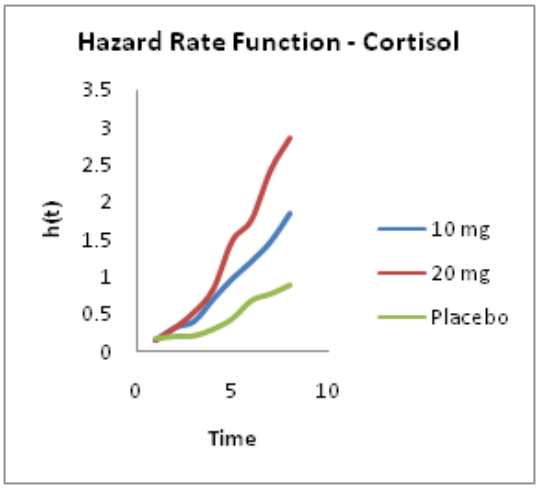

Figure 3.3

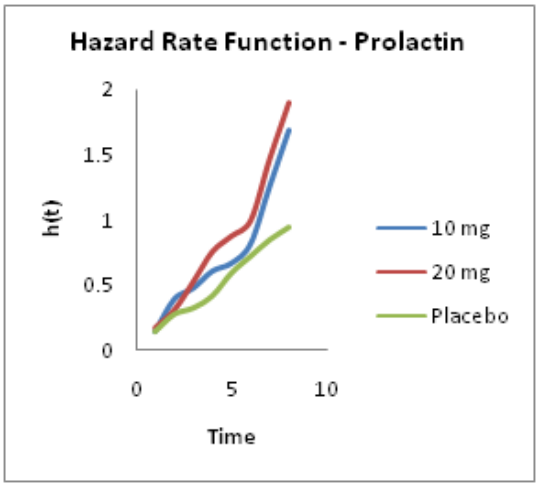

Figure 3.4

Hazard Rate Functions for the second internal state during the speech of Plasma cortisol and Prolactin Levels:

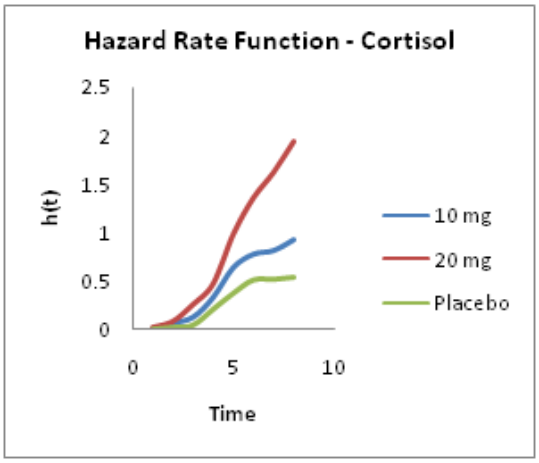

Figure 3.5

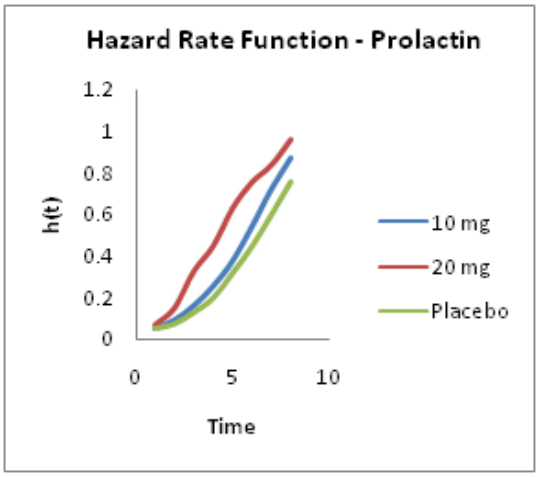

Figure 3.6

Sub – Models of Transmuted Weibull Distribution

i) Transmuted Modified Weibull Distribution:

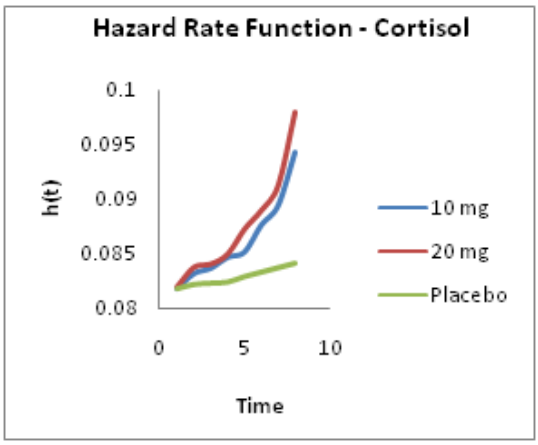

Figure 3.7

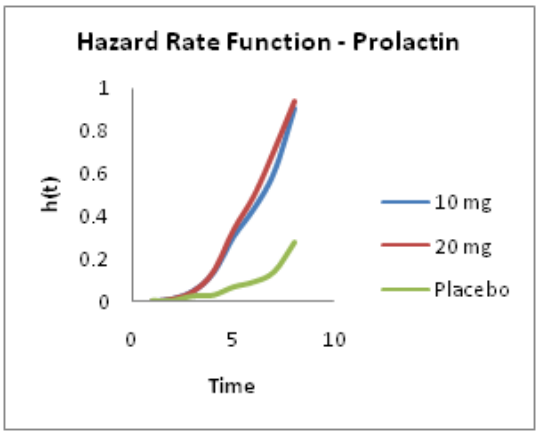

Figure 3.8

ii) Additive Weibull Distribution:

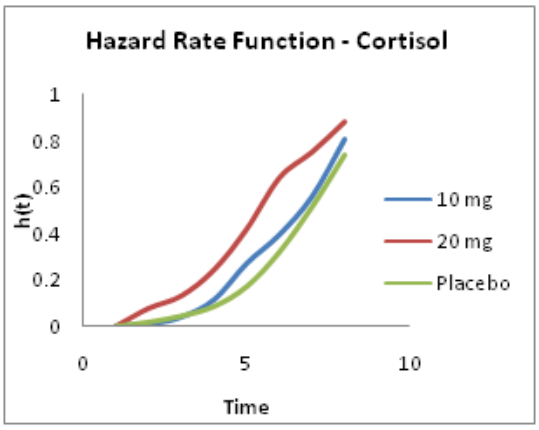

Figure 3.9

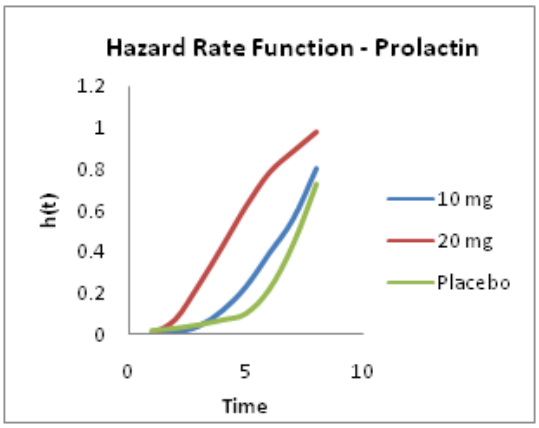

Figure 3.10

4. Conclusion

The preceding evidence indicates that anxiety and panic are qualitatively different emotional states, which are related to the defense reactions to potential and proximal threat, respectively. In regard to stress hormones, the analyzed data suggest that while anxiety activates both the HPA and the sympatho-adrenal axes, the panic attack causes major sympathetic activation, but has little effect on the HPA axis. Here the organism tends to keep its internal states within narrow limits through specific adaptive responses that tend to correct any provoked imbalance. Therefore, in this paper the idea of finite state continuous time markov chain is used to find out the internal states between the states P and F for the Simulated Public Speaking Test for Figure 2.2.2 in the application part. The hazard rate functions for these two internal states are find out for the plasma cortisol and prolactin levels as in Figures 3.3, 3.4, 3.5 & 3.6 and are compared with the hazard rate function for the whole time practical session as in Figures 3.1 & 3.2.

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