Non-Parametric Inferential Methods
- Treating Tardive Dyskinesia using Deanol

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Contents

Abstract

This report discusses some non-parametric inferential techniques to inquire the effectiveness of a drug Deanol in treating movement disorder-*Tardive Dyskinesia*. In the experiment, Deanol and a Placebo treatment were given to 14 patients and improvements of each patients were monitored for 4 weeks. After the testing period, Total Severity Index (TSI) score of each patients were recorded. TSI score measures the improvement/reduction in symptoms. Larger the TSI, greater the improvement. The associated data sets have been taken from Penovich et al. (1978). In the Paper, it had been observed patient conditions improved significantly from baseline scores while receiving both Deanol and Placebo, but there was no notable difference observed between the two treatments.

1 Objective

Using non-parametric inferential techniques evaluate the effectiveness of the drug Deanol in reducing symptoms of *Tardive Dyskinesia*.

2 Experimental Data

Patient	TSI Score	
	Deanol	Placebo
1	12.4	9.2
2	6.8	10.2
3	12.6	12.2
4	13.2	12.7
5	12.4	12.1
6	7.6	9.0
7	12.1	12.4
8	5.9	5.9
9	12.0	8.5
10	1.1	4.8
11	11.5	7.8
12	13.0	9.1
13	5.1	3.5
14	9.6	6.4

Summary Statistics	**Deanol**	**Placebo**
count	14	14
mean	9.66	8.84
std	3.75	2.94
min	1.10	3.50
25%	7.00	6.75
50%	11.75	9.05
75%	12.40	11.62
max	13.20	12.70

Note: A Placebo is an inert physical substance or treatment with no therapeutic value, such as sugar pills. In drug testing, one group of people get the tested drug, while the others receive a placebo (fake drug), to resemble the active medication through real drug. If the researchers found same improvement from both the groups, then drug is consider as non-effective to the respective disorder.

3 Non-Parametric Inference Tests

3.1 Wald-Wolfwitz 2-sample Runs Test

Objective: Detect Non-Randomness. To investigate whether or not the two sets of TSI score coming from an identical distribution.

Procedure: $X_1, \cdots, X_{n_1}$, r.v.s from a continuous population $F_X(x)$
$Y_1, \cdots, Y_{n_2}$, r.v.s from a continuous population $G_Y(y)$

$H_0 : F_X(x) = G_Y(x)\ \forall\ x$
$H_a : F_X(x) \neq G_Y(x)\ for\ some\ x$

Test Statistics: R = no. of runs in the combined ordered arrangement of n_1 X & n_2 Y r.v.s

For Large Sample,
Test Statistic,

$$Z = \frac{R - \mu_R}{\sigma_R}$$

where, μ_R is the expected number of runs, and σ_R is the standard deviation of the number of runs.

$$\mu_R = \frac{2n_1n_2}{n_1 + n_2} + 1$$

$$\sigma_R^2 = \frac{2n_1n_2(2n_1n_2 - n_1 - n_2)}{(n_1 + n_2)^2(n_1 + n_2 + 1)}$$

Significance Level: α
Rejection Region: $R \leq \mu_R + z_\alpha \cdot \sigma_R$,

p-value $= P\big(Z \leq \frac{r-\mu_R}{\sigma_R}\big) \leq \alpha$

Problem of Ties: Ties are solved by an arrangement giving maximum runs. (Gibbons and Chakraborti (2014))

Results:

Test Statistic Value, R	: 19
Z-score	: 1.597
p-value	: 0.944834

Conclusion: Deanol doesn't differ from the Placebo in regards to TSI. (Not enough evidence to reject Null Hypothesis)

Significance Level	α	Conclusion (p > α)
90 %	0.1	Fail to Reject H_0
95 %	0.05	Fail to Reject H_0
99 %	0.01	Fail to Reject H_0

3.2 Kolmogorov-Smirnov 2-sample Test

Objective: Detect Non-Randomness. To investigate whether or not the two sets of TSI score coming from an identical distribution.

Procedure: $X_{(1)}, ...X_{(n_1)}$, order statistic from a continuous population F_X
$Y_{(1)}, ...Y_{(n_2)}$, order statistic from a continuous population G_Y

$H_0 : F_X(x) = G_Y(x) \; \forall \; x$
$H_a : F_X(x) \neq G_Y(x) \; for \; some \; x$

Test Statistics: $D_{n_1,n_2} = \max_x |S_{n_1}(x) - S_{n_2}(x)|$

where $S_{n_1}(x)$ & $S_{n_2}(x)$, are the empirical distribution functions of X, Y respectively. Empirical distribution is defines as,

$$S_n(z) = \begin{cases} 0 & if \; z < Z_{(1)} \\ k/n & if \; Z_{(k)} \leq z \leq Z_{(k+1)} \\ 1 & if \; z \geq Z_{(n)} \end{cases}$$

Significance Level: α
Rejection Region: $D_{n_1,n_2} \geq c_\alpha$, satisfying
$P(D_{n_1,n_2} \geq c_\alpha) \leq \alpha$, i.e p-value $\leq \alpha$

Results:
Test Statistic Value : 0.286
p-value : 0.540740

Conclusion: No distinction between Deanol and Placebo in regards to TSI. (Not enough evidence to support that the two sets of TSI score coming from different distribution)

Significance Level	α	Conclusion (p > α)
90 %	0.1	Fail to Reject H_0
95 %	0.05	Fail to Reject H_0
99 %	0.01	Fail to Reject H_0

3.3 Median Test

Objective: To investigate the median TSI score of Deanol drug is less or greater than the Placebo treatment.

Procedure: $X_1, \cdots, X_{n_1}$, order statistic from a continuous population F_X
$Y_1, \cdots, Y_{n_2}$, order statistic from a continuous population G_Y

$H_0 : M_X = M_Y$
$H_{a_1} : M_X < M_Y$
$H_{a_2} : M_X > M_Y$
$H_{a_3} : M_X \neq M_Y$,

where M_X & M_Y are the median of X & Y sample respectively.

Test Statistics: $U = \sum_{i=1}^{n_1} I\{X_i < M\}$

For Large Sample,
Test Statistic,

$$Z = \frac{U - n_1 t/N}{[n_1 n_2 t(N-t)/N^3]^{1/2}}$$

where, $N = n_1 + n_2$, and
$$t = \begin{cases} N/2 & if\ N\%2 = 0 \\ (N-1)/2 & if\ N\%2 \neq 0 \end{cases}$$

Alternative	Rejection Region	p-value
H_{a_1}	$Z \geq z_\alpha$	$P(Z \geq z)$
H_{a_2}	$Z \leq -z_\alpha$	$P(Z \leq z)$
H_{a_3}	$Z \leq -z_{\alpha/2}$ or $Z \geq z_{\alpha/2}$	2(smaller of the above)

Results:

Test Statistic Value, U : 5
Z-score : -1.51186

Alternative	p-value
H_{a_1}	0.93471
H_{a_2}	0.06529
H_{a_3}	0.13057

Conclusion: With 5 % Type I error, median TSI of the Deanol doesn't differ from the median TSI of the Placebo. With 10 % Type I error, median TSI of the Deanol found to be more than median TSI of the Placebo.

Significance Level	α	Alternative	Conclusion
		H_{a_1}	Fail to Reject H_0
90 %	0.1	H_{a_2}	Reject H_0, (p-value $< \alpha$)
		H_{a_3}	Fail to Reject H_0
		H_{a_1}	Fail to Reject H_0
95 %	0.05	H_{a_2}	Fail to Reject H_0
		H_{a_3}	Fail to Reject H_0

3.4 Mann-Whitney Test

Objective: To investigate whether or not two sets of TSI score coming from an identical distribution (i.e. Deanol is more or less defensive to Placebo).

Procedure: $X_1, \cdots, X_{n_1}$, order statistic from a continuous population F_X
$Y_1, \cdots, Y_{n_2}$, order statistic from a continuous population G_Y

$H_0 : F_X(x) = G_Y(x) \; \forall \; x$
$H_a : F_X \neq G_Y$

Test Statistics: $U = \sum_{i=1}^{n_1} \sum_{j=1}^{n_2} D_{ij}$

$$\text{where } D_{ij} = \begin{cases} 1 & X_i > Y_j \\ 0.5 & X_i = Y_j \\ 0 & X_i < Y_j \end{cases}$$

For Large Sample,
Test Statistic,

$$Z = \frac{U - n_1 n_2/2}{\sqrt{n_1 n_2 (n_1 + n_2 + 1)/12}}$$

Significance Level: α
Rejection Region: $Z \leq -z_{\alpha/2}$ or $Z \geq z_{\alpha/2}$
p-value $= 2 \cdot P(Z \geq z) \leq \alpha$

Results:

Test Statistic Value, U : 118
Z-score : 0.91895
p-value : 0.35812

Conclusion: Deanol doesn't differ from the Placebo in regards to TSI. No distinction between the two treatments.

Significance Level	α	Conclusion (p $> \alpha$)
90 %	0.1	Fail to Reject H_0
95 %	0.05	Fail to Reject H_0
99 %	0.01	Fail to Reject H_0

3.5 Paired-Sample Problem

Definition of the Rank:
Rank of any x_i in a set of N different observations is defined as,

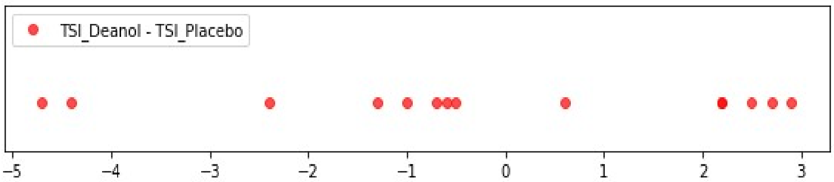
$$rank(x_i) = \sum_{k=1}^{N} \sigma(x_i - x_k)$$

where,

$$\sigma(x) = \begin{cases} 1, & if\ x \geq 0 \\ 0, & if\ x < 0 \end{cases}$$

3.5.1 Signed Rank Test

Objective: To investigate if the median of the difference of TSI score for the people treated Deanol and Placebo respectively, exceeds by more than 1.



Procedure: $X_1, \cdots, X_n$, order statistic from a continuous population F_X
$Y_1, \cdots, Y_n$, order statistic from a continuous population G_Y
For each pair of random sample, (X_i, Y_i), $\quad i = 1, 2, \cdots, n$
Define,

$$D_i = X_i - Y_i$$

$H_0 : m_D = m_o(= 1)\ \forall\ (x_i, y_i)$
$H_a : m_D > m_o$, where m_D is the median of D

Test Statistics: $T = \sum_{i=1}^{n} sgn(D_i - m_o) \cdot rank(|D_i - m_o|)$

$$\text{where } sgn(x) = \begin{cases} 1, & x > 0 \\ 0, & x = 0 \\ -1, & x < 0 \end{cases}$$

For Large Sample,
Test Statistic,

$$Z = \frac{T}{\sqrt{\frac{n(n+1)(2n+1)}{6}}}$$

Significance Level: α

Rejection Region: $T \geq z_\alpha \cdot \sqrt{\frac{n(n+1)(2n+1)}{6}}$

p-value $= P\big(Z \geq t/\sqrt{\frac{n(n+1)(2n+1)}{6}}\big) \leq \alpha$

Results:

Test Statistic Value, T : -4
Z-score : -0.12555
p-value : 0.54996

Conclusion: There is not sufficient evidence to support that the median of the difference of TSI score for the people treated Deanol and Placebo respectively, exceeds by more than 1.

Significance Level	α	Conclusion (p > α)
90 %	0.1	Fail to Reject H_0
95 %	0.05	Fail to Reject H_0
99 %	0.01	Fail to Reject H_0

3.6 Location Problem

It refers to the *location alternative*, that the populations are of the same nature but with a different central tendency.

Assume two independent r.v.s,
$X_1, \cdots, X_m$, order statistic from a continuous population F_X
$Y_1, \cdots, Y_n$, order statistic from a continuous population G_Y

$$\begin{aligned} H_0 &: \quad G_Y(x) = F_X(x) && \forall\ x \\ H_a &: \quad G_Y(x) = F_X(x - \theta) && \forall\ x \textit{ and some } \theta \neq 0 \end{aligned}$$

3.6.1 Wilcoxon Rank Sum Test

Objective: To investigate the TSI score of Deanol drug is greater than the Placebo treatment.

Procedure: $X_1, \cdots, X_{n_1}$, order statistic from a continuous population F_X
$Y_1, \cdots, Y_{n_2}$, order statistic from a continuous population G_Y
The combined ordered sample is, $\mathbf{Z} = (Z_1, \cdots Z_N),\ N = n_1 + n_2$.

$H_0 : \theta = 0$
$H_{a_1} : \theta < 0$
$H_{a_2} : \theta > 0$
$H_{a_3} : \theta \neq 0$

Test Statistics: $W_N = \sum_{i=1}^{N} i \cdot Z_i$

where $Z_i = \begin{cases} 1, & if\ Z_i \in \mathbf{X} \\ 0, & if\ Z_i \in \mathbf{Y} \end{cases}$

For Large Sample,
Test Statistic,

$$Z = \frac{W_N - \mu_{W_N}}{\sigma_{W_N}}$$

where, μ_{W_N} & σ_{W_N} are the expectation and standard deviation of rank-sum of $X_i's$ respectively.

$$\mu_{W_N} = \frac{n_1(N+1)}{2}$$

$$\sigma^2_{W_N} = \frac{n_1 n_2(N+1)}{12}$$

Alternative	Rejection Region	p-value
H_{a_1}	$W_N \geq \mu_{W_N} + 0.5 + z_\alpha \cdot \sigma_{W_N}$	$1 - \Phi(\frac{W_N - 0.5 - \mu_{W_N}}{\sigma_{W_N}})$
H_{a_2}	$W_N \leq \mu_{W_N} - 0.5 - z_\alpha \cdot \sigma_{W_N}$	$\Phi(\frac{W_N + 0.5 - \mu_{W_N}}{\sigma_{W_N}})$
H_{a_3}	Above with z_α replaced by $z_\alpha/2$	$2 \cdot \min\{p_{H_{a_1}}, p_{H_{a_2}}\}$

Results: Since **p**-value $\to 0/1$, normal approximation with continuity correction of 0.5 is used to find the rejection region and **p**-values.

Test Statistic Value, W_N : 223

Alternative	p-value
H_{a_1}	0.18513
H_{a_2}	0.82689
H_{a_3}	0.34623

Conclusion: Efficacy of the Deanol doesn't differ from the Placebo. (Not enough evidence to show Deanol works better than Placebo treatment).

Significance Level	α	Alternative	Conclusion
90 %	0.1	H_{a_1}	Fail to Reject H_0
		H_{a_2}	Fail to Reject H_0
		H_{a_3}	Fail to Reject H_0
95 %	0.05	H_{a_1}	Fail to Reject H_0
		H_{a_2}	Fail to Reject H_0
		H_{a_3}	Fail to Reject H_0

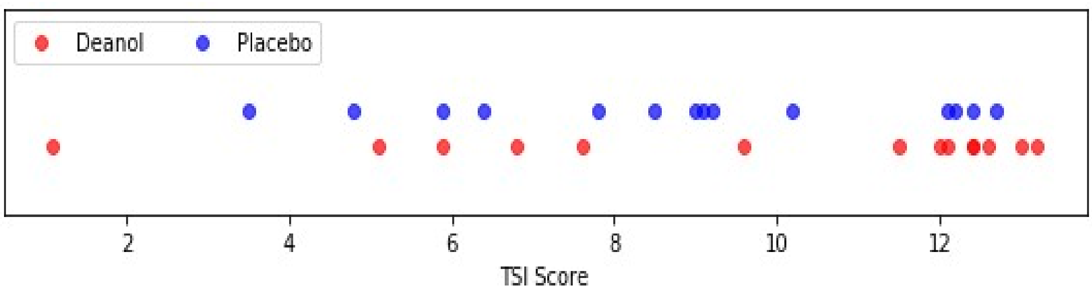
3.7 Scale Problem

It refers to the *scale alternative*, that the populations are of the same nature but with a compressed or amplified scale.

Assume two independent r.v.s,
$X_1, \cdots, X_m$, order statistic from a continuous population F_X
$Y_1, \cdots, Y_n$, order statistic from a continuous population G_Y

$$\begin{aligned} H_0 :&\quad G_Y(x) = F_X(x) && \forall\ x \\ H_a :&\quad G_Y(x) = F_X(\theta x) && \forall\ x \textit{ and some } \theta \neq 1,\ \theta > 0 \end{aligned}$$

3.7.1 Mood Test



Objective: To investigate the dispersion of TSI score of the patients treated with Deanol.

Procedure: $X_1, \cdots, X_{n_1}$, order statistic from a continuous population F_X
$Y_1, \cdots, Y_{n_2}$, order statistic from a continuous population G_Y
The combined ordered sample is, $\mathbf{Z} = (Z_1, \cdots Z_N),\ N = n_1 + n_2$.

$H_0 : \theta = 1$
$H_a : \theta \neq 1$

Test Statistics: $M_N = \sum_{i=1}^{N} \left(i - \frac{N+1}{2}\right)^2 \cdot Z_i$

where $Z_i = \begin{cases} 1, & if\ Z_i \in \mathbf{X} \\ 0, & if\ Z_i \in \mathbf{Y} \end{cases}$

For Large Sample,
Test Statistic,

$$Z = \frac{M_N - \mu_{M_N}}{\sigma_{M_N}}$$

where,

$$\mu_{M_N} = \frac{n_1(N^2 - 1)}{12}$$

$$\sigma^2_{M_N} = \frac{n_1 n_2 (N+1)(N^2 - 4)}{180}$$

Significance Level: α
Rejection Region: $Z \leq -z_{\alpha/2}$ or $Z \geq z_{\alpha/2}$
p-value $= 2 \cdot P(Z \geq z) \leq \alpha$

Results: Test Statistic Value, M_N : 1827

Conclusion: Since, M_N is large. Therefore, TSI score of the patients treated with Deanol are widely dispersed.

4 Measures of Association

4.1 Kendall's Tau Coefficient

Objective: To inspect the possible association in the two sets of TSI score.

Procedure: $X_1, \cdots, X_n$, order statistic from a continuous population F_X
$Y_1, \cdots, Y_n$, order statistic from a continuous population G_Y
For each set of pairs $(X_i, Y_i), (X_j, Y_j)$ of the sample observations, define

$$A_{ij} = sgn(X_i, X_j)\ sgn(Y_i, Y_j), \quad where\ sgn(x) = \begin{cases} 1, & x > 0 \\ 0, & x = 0 \\ -1, & x < 0 \end{cases}$$

H_0 : X & Y are independent
H_{a_1} : Positive dependence
H_{a_2} : Negative dependence
H_{a_3} : Non-Independence

Test Statistics: $T = (C - Q)/\binom{n}{2}$

where C & Q are the number of positive and negative $A_{ij},\ for\ 1 \leq i < j \leq n, respectively.$

For Large Sample,
Test Statistic,

$$Z = \frac{3\sqrt{n(n-1)}T}{\sqrt{2(2n+5)}}$$

Alternative	Rejection Region	p-value
H_{a_1}	$T \geq z_\alpha \sqrt{2(2n+5)}/3\sqrt{n(n-1)}$	$P(z \geq \frac{3t\sqrt{n(n-1)}}{\sqrt{2(2n+5)}})$
H_{a_2}	$T \leq z_\alpha \sqrt{2(2n+5)}/3\sqrt{n(n-1)}$	$P(z \leq \frac{3t\sqrt{n(n-1)}}{\sqrt{2(2n+5)}})$
H_{a_3}	Both above with $z_{\alpha/2}$	2(smaller of the above)

Results:	Test Statistic Value, T	: 0.61879
	Z-score	: 3.0827

Alternative	p-value
H_{a_1}	0.00103
H_{a_2}	0.99897
H_{a_3}	0.00205

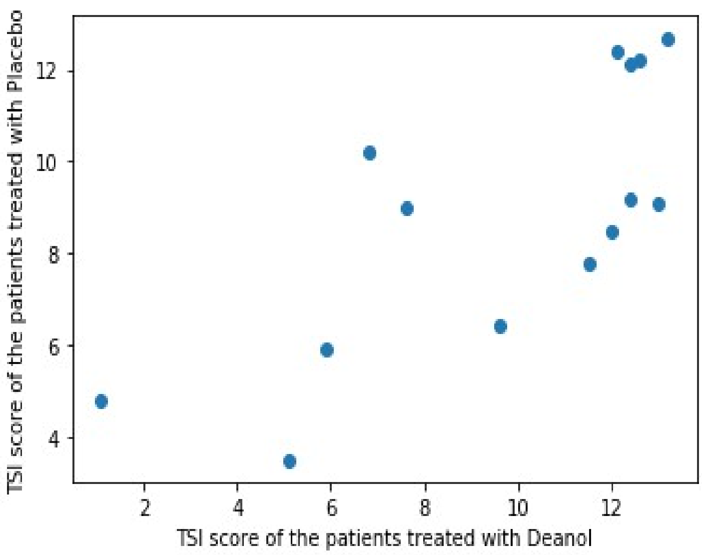
Conclusion: With 5% Type I error, we conclude that TSI score of Deanol and Placebo are positively correlated.

Significance Level	α	Alternative	Conclusion
90 %	0.1	H_{a_1}	Reject H_0
		H_{a_2}	Fail to Reject H_0
		H_{a_3}	Reject H_0
95 %	0.05	H_{a_1}	Reject H_0
		H_{a_2}	Fail to Reject H_0
		H_{a_3}	Reject H_0

4.2 Spearman's Coefficient of Rank Correlation

Objective: To inspect the possible association in the two sets of TSI score..

Procedure: $X_1, \cdots, X_n$, order statistic from a continuous population F_X
$Y_1, \cdots, Y_n$, order statistic from a continuous population G_Y



H_0 : X & Y are independent
H_{a_1} : Positive dependence
H_{a_2} : Negative dependence
H_{a_3} : Non-Independence

Test Statistics:

$$R = \frac{\sum_{i=1}^{n}(R_i - \bar{R})(S_i - \bar{S})}{\sqrt{\sum_{i=1}^{n}(R_i - \bar{R})^2 \ \sum_{i=1}^{n}(S_i - \bar{S})^2}}$$

where $R_i = rank(X_i)$ & $S_i = rank(Y_i)$
$\bar{R} = \sum_{i=1}^{n} R_i \ and \ \bar{S} = \sum_{i=1}^{n} S_i$

For Large Sample,
Test Statistic,

$$Z = \frac{R}{\sqrt{n-1}}$$

Alternative	Rejection Region	p-value
H_{a_1}	$R \geq z_\alpha \sqrt{n-1}$	$P(Z \geq r/\sqrt{n-1})$
H_{a_2}	$R \leq -z_\alpha \sqrt{n-1}$	$P(Z \leq r/\sqrt{n-1})$
H_{a_3}	Both above with $z_{\alpha/2}$	2(smaller of the above)

Results:

Test Statistic Value, R	:	0.78414
Z-score	:	0.21748

Alternative	p-value
H_{a_1}	0.41392
H_{a_2}	0.58608
H_{a_3}	0.82783

Conclusion: Not sufficient evidence to support dependence between TSI score of the patients treated with Deanol and Placebo.

Significance Level	α	Alternative	Conclusion
90 %	0.1	H_{a_1}	Fail to Reject H_0
		H_{a_2}	Fail to Reject H_0
		H_{a_3}	Fail to Reject H_0
95 %	0.05	H_{a_1}	Fail to Reject H_0
		H_{a_2}	Fail to Reject H_0
		H_{a_3}	Fail to Reject H_0

5 Observations

a. Linear relationship between Mann-Whitney (U) test and Wilcoxon Rank-Sum (W_N) test:

$$U = W_N - \frac{m(m+1)}{2}, \quad \textit{where } m \textit{ is the number of observations of } X.$$

From 3.4 and 3.6.1, we have U = 118 and W_N = 223. Verified:

$$W_N - U = 105 = \frac{14 \cdot (14+1)}{2} = \frac{n_1 \cdot (n_1+1)}{2}$$

b. From 3.3 and 3.4, we observed Mann-Whitney Test performs better than Median Test. Verified: Asymptotic Relative Efficiency (ARE) of Mann-Whitney Test is more than the Median Test.

c. In 3.7.1-figure, we observed outliers in TSI score of the patients treated with Deanol. Verified by Mood Test (i.e large dispersion).

d. In 4.2-figure, we observed positive dependence between the two sets of TSI score. We obtained similar correlation using Kendall's Tau coefficient.

e. Spearman's rho calculations based on the deviations, i.e. sensitive to outliers. And TSI score of patients treated with Deanol contain outliers, Therefore, we failed to show positive dependence using Spearman's rho.

6 Conclusion

There is not enough evidence to support that treating *Tardive Dyskinesia* using Deanol provide significant improvement as compared to Placebo treatment. Conclusion is consistent with the Penovich et al. (1978) findings (see *Abstract*).

References

Gibbons, J. D. and Chakraborti, S. (2014). *Nonparametric Statistical Inference: Revised and Expanded*. CRC press.

Penovich, P., Morgan, J. P., Kerzner, B., Karch, F., and Goldblatt, D. (1978). Double-Blind Evaluation of Deanol in Tardive Dyskinesia. *JAMA*, 239(19):1997–1998.