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*Full Length Research Paper*

## **Anti-Ulcer Effect of Risperidone in Rats**

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### **ABSTRACT**

Risperidone is a second-generation atypical antipsychotic drug currently used for the management of psychosis in schizophrenia, delusional psychosis and psychotic depression an action ascribed to its being a dopamine antagonist possessing anti-serotonergic, anti-adrenergic and anti-histaminergic properties. However, there are indications that risperidone has gastroprotective effect. Thus this study was carried out to examine the effect of risperidone on stress-induced and indomethacin-induced ulcers in the rats. Rats were treated with risperidone (0.1mg/kg, 0.3mg/kg and 0.5mg/kg) orally once daily for 21 days before assessing for ulcer using water immersion restraint stress (WIRS), starvation and indomethacin-induced ulcer models. Risperidone caused a significant dose-dependent reduction in gastric ulcer scores [0.1mg/kg (3.5±0.2), 0.3mg/kg (1.9±0.3), 0.5mg/kg (1.2±0.2)] compared with control (5.6±0.3) in WIRS; [0.1mg/kg (4.0±0.3), 0.3mg/kg (2.3±0.2), 0.5mg/kg (1.8±0.2)] compared with control (6.1±0.3) in starvation and [0.1mg/kg (4.9±0.3), 0.3 mg/kg (2.0±0.2), 0.5 mg/kg (1.3±0.2)] compared with control (6.4±0.4) in indomethacin-induced ulcer models. These findings suggest that risperidone has gastric anti-ulcer property. However, more detailed studies are necessary to confirm the relevance of this finding and its implications in clinical settings.

**Key words:** risperidone, gastric ulcer, starvation, stress

### **INTRODUCTION**

Non-steroidal drugs, cigarettes, alcohol usage, *Helicobacter pylori*, and stress have been shown to contribute to gastric ulcer formation (Mózsik, and Jávör, 1988; Davies *et al.* 1994; Ding *et al.*, 1998; Hooderwerf and Pasricha, 2006). The successful treatment of gastric lesion depends on augmentation of the defensive factors of the gastric mucosa and blockage of acid secretion (Borelli and Izzo, 2000). However, the goals of treating gastric ulcer include relief of pain, healing of the ulcer and prevention of its recurrence (Sostres and Lanás,

2011). Many of the anti-ulcer drugs in use have been found to have adverse effects and there is recurrent infection after a few weeks (Chan and Leung, 2002). Stress as one of the aggressive factors in peptic ulcer formation, underlies many other diseases apart from ulcers and, thus stress is one of the most commonly used methods to produce ulcer models (Kwiecień *et al.*, 2007; Brzozowski *et al.*, 2008). Moreover, antidepressants Ries *et al.*, (1984) and anxiolytics (Shrivastava and Siegel, 1984; Haggerty and Drossman, 1985) were reported to significantly reduce stress ulcer formation, perhaps to a greater extent than that seen with traditional

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therapies such as cimetidine and antacids (Shrivastava *et al.*, 1985). Also several novel arylpiperazine serotonin 1A receptor (5HT<sub>1</sub>-A) agonists developed as anxiolytics, has been reported to have antisecretory and gastroprotective effects in rats (Glavin *et al.*, 1998). Antipsychotics especially risperidone though reported to have gastroprotection activity have not been fully documented. Thus, this study was carried out to examine the likely anti-ulcer effect of risperidone in male Wistar rats.

## MATERIALS AND METHODS

### Experimental animals

Male Wistar rats weighting between 180 and 210g were used in the study. The animals were purchased from the Central animal house, College of Medicine, University of Ibadan, Nigeria and housed in plastic cages at room temperature. They were fed with normal rats' pellet from Ladokun Feeds Industry, Ibadan and water was provided ad libitum. They were acclimatized for two weeks before the experiment. The laboratory animals were handled in accordance with the National Institutes of Health (NIH) principles of Laboratory Animal Care and Use.

### Drugs and chemicals

Risperidone (Jiangsu Suzhong Haixin Pharm CO, China), Indomethacin ((Merck, Sharp & Dohme, Canada). The drugs were dissolved in distilled water, while a pinch of sodium carbonate (Na<sub>2</sub>CO<sub>3</sub>) was added to dissolve indomethacin. Doses of risperidone and indomethacin used in this study were chosen based on the information obtained from previous studies (Oluwole *et al.*, 2008; Saxena and Sanjay, 2011).

### Experimental procedures

**Water immersion restraint stress-induced (WIRS) ulcer:** Gastric ulcers induced by water-immersion stress (WIS) in rats or mice are known to resemble human peptic ulcers, both grossly and histopathologically (Byun *et al.*, 2007). Male Wistar rats were randomly distributed into 4 treatment groups (n=6). Animals in group 1 received distilled water and acted as control. Groups 2, 3 and 4 were given risperidone (0.1mg/kg, 0.3 mg/kg and 0.5 mg/kg orally). The drug was given once daily for 21 consecutive days. Thirty minutes after the last treatment of each rat in each group, the test on WIRS was commenced. Briefly, each animal was placed in a restraint device and immersed up to its xiphoid process in a 22°C water bath for 17 hours according to earlier methods (Brodie and Hanson, 1960; Byun *et al.*, 2007). The rats were later sacrificed by cervical dislocation, the stomachs removed and the glandular portion of the each

stomach opened by cutting along the whole length of the greater curvature, turned inside out and pinned to a cork mat. Macroscopic examinations of the washed stomachs were carried out using a magnifying hand lens and gastric mucosal lesion was assessed as earlier described (Desai *et al.*, 1999). Morphometric studies were performed using Olympus light microscope (x100) fitted with Casio digital camera and Motic plus China, 2000 software.

**Indomethacin- induced gastric ulceration:** Male Wistar rats were randomly distributed into 4 treatment groups as indicated above. Group 1 received distilled water and acted as control. Groups 2, 3 and 4 were given risperidone (0.1mg/kg, 0.3 mg/kg and 0.5 mg/kg orally). Drug was administered once daily for 21 consecutive days. The animals were fasted for 24 hours, but allowed free access to water. The method of gastric ulceration induction adopted was that described in previous works (Oluwole *et al.*, 2008). Indomethacin at 40 mg/kg BW was administered subcutaneously to all the animals in all the groups. After 4 hours, the animals were sacrificed by cervical dislocation and their stomachs removed, opened by cutting along the whole length of the greater curvature, turned inside out and then pinned to a cork mat. This was moistened with normal saline to prevent autolysis. Scoring of gastric ulceration was by the previously reported methods (Alphin and Ward, 1967; Elegbe and Bamgbose, 1976).

**Starvation – induced ulceration:** The animals were deprived of food however allowed access to water ad libitum for the last 6 days within the 21 days risperidone treatment. On the 6th day of food deprivation, the animals were sacrificed by cervical dislocation. Their stomachs were removed, opened by cutting along the whole length of the greater curvature, turned inside out and then pinned to a cork mat. This was moistened with normal saline to prevent autolysis. The method used for scoring ulcer was as earlier described (Elegbe and Bamgbose, 1976). Macroscopic examinations of the washed stomachs were carried out with a magnifying hand lens.

### Statistical analysis

The data were analyzed using Graphpad prism software version 5 and were expressed as Mean ± SEM (Standard Error of Mean). Statistical analysis of data was done using one-way analysis of variance (ANOVA) and Student's t-test for paired data. P-values less than 0.05 ( $p \leq 0.05$ ) were considered statistically significant.

## RESULTS

### Effect of risperidone on water immersion restraint stress-induced gastric ulceration

The effect of risperidone on water immersion restraint stress-induced gastric ulceration is as shown in Table 1. There was significant dose-dependent increase in ulcer inhibition in all the risperidone treated animals compared to the control ( $p \leq 0.05$ ). The other parameters measured showed significant decreases compared to the control. This shows an increase in degree of gastroprotection.

### Effect of risperidone on indomethacin-induced gastric ulceration

The effect of risperidone on indomethacin-induced gastric ulceration as measured by ulcer scores, ulcer area ( $\mu\text{m}^2$ ), percentage ulcer inhibition and of ulcer area (%) are shown on Table 2. The percentage ulcer inhibition increased in the risperidone treated groups in a dose-dependent manner. There was also significant dose – dependent decrease in other parameters measured in the risperidone treated groups compared to the control ( $p \leq$

0.05). This demonstrates a significant increase in degree of gastroprotection

### Effect of risperidone on starvation-induced gastric ulceration

Effects of risperidone on starvation-induced gastric ulceration in rats are shown in Figure 3 and Table 3. Risperidone administered once daily for 21 days produced a dose-dependent decrease in the ulcer score with increase in dose of risperidone. These decreases in all the risperidone treated animals are significantly different compared to the control ( $p \leq 0.05$ ). This is indicative of an increase in degree of protection with increase in the dose of risperidone.

### Histological changes in treated groups

The photo plates showed the effects of risperidone on the three different ulcer models ((indicated by arrows). There were evidences of reduction in gastric ulceration in all the risperidone treated rats groups compared to the controls.

**Table 1:**  
Effect of risperidone on water immersion restraint stress-induced gastric ulceration

Treatment	Ulcer score <sup>a</sup>	Inhibition of ulceration (%) <sup>b</sup>	Ulcer Area ( $\mu\text{m}^2$ ) ( $10^5$ )	% of Ulcer Area	Perimeter ( $\mu\text{m}$ ) ( $10^3$ )
Distilled water (Control)	6.06 ± 0.32	-	36.54	-	10.85
Risperidone (0.1mg/kg)	4.00 ± 0.30*	33.99	18.84	51.57 *	6.71
Risperidone (0.3mg/kg)	2.25 ± 0.21*	62.87	3.70	10.13*	5.99
Risperidone (0.5mg/kg)	1.75 ± 0.21*	71.12	0.85	2.33*	2.45

<sup>a</sup>Values represent the mean ± SEM, for 5 animals per group. \*  $p < 0.05$  with control (student t-test followed by ANOVA).

**Table 2:**  
Effect of risperidone on indomethacin-induced gastric ulceration

Treatment	Ulcer score <sup>a</sup>	Inhibition of ulceration (%) <sup>b</sup>	Ulcer Area ( $\mu\text{m}^2$ ) ( $10^5$ )	% of Ulcer Area	Perimeter ( $\mu\text{m}$ ) ( $10^3$ )
Distilled water (Control)	6.44 ± 0.36	-	26.62	-	11.85
Risperidone (0.1mg/kg)	4.94 ± 0.26*	23.30*	6.37*	23.91 *	4.72*
Risperidone (0.3mg/kg)	2.00 ± 0.19*	68.93*	4.89*	18.38*	4.37*
Risperidone (0.5mg/kg)	1.31 ± 0.19*	79.61*	2.42*	9.12*	3.99*

<sup>a</sup>Values represent the mean ± SEM, for 5 animals per group. \*  $p < 0.05$  with control (student t-test followed by ANOVA).

*Effect of risperidone on WIRS-induced gastric ulcer :* Plates 1 and 2 showed haemorrhagic ulcers and histological profile in A (control) compared to the risperidone treated animal, A (0.1 mg/kg), B (0.3 mg/kg) and C (0.5 mg/kg) in WIRS. Fewer numbers of haemorrhagic ulcers were recorded in Plate B, C and D. The ulceration in the control and risperidone- treated rat groups are indicated with arrows

*Effect of risperidone on indomethacin-induced gastric ulceration*  
Plate 3 and 4 shows ulcer lesions (indicated by arrows) of the control (A) compared to the risperidone treated

animal, A (0.1mg/kg), B (0.3mg/kg) and C (0.5mg/kg). Plate 6D is almost free of ulcers. The ulceration decreases as the dose of risperidone increased compared to the control

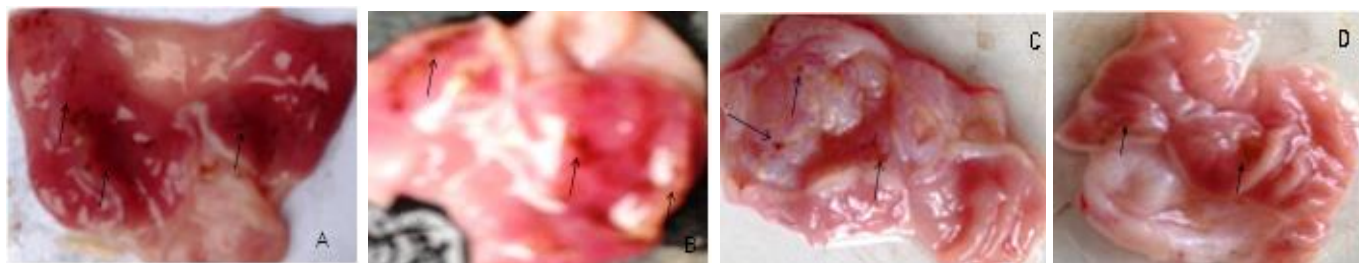
*Effect of risperidone on starvation-induced gastric ulceration*

Plates 5 and 6 shows ulcer lesions of the control (A) compared to the risperidone treated animals, B (0.1mg/kg), C (0.3mg/kg) and D (0.5mg/kg) indicated by arrows. There are decreases in ulceration as the dose of risperidone increased compared to the control

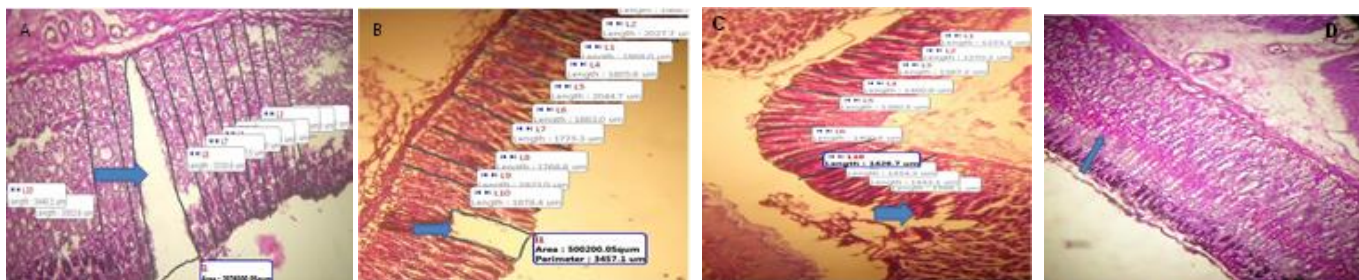
**Table 3:**  
Effect of risperidone on starvation - induced ulceration

Treatment	Ulcer score <sup>a</sup>	Inhibition of ulceration (%) <sup>b</sup>	Ulcer Area (µm) <sup>2</sup> (10 <sup>5</sup> )	% of Ulcer Area	Perimeter (µm) (10 <sup>3</sup> )
Distilled water (Control)	5.56 ± 0.32	-	20.77	-	8.43
Risperidone (0.1mg/kg)	3.50 ± 0.19*	37.05*	5.00*	24.09 *	3.46*
Risperidone (0.3mg/kg)	1.88 ± 0.30*	66.19*	2.28*	11.00*	2.89*
Risperidone (0.5mg/kg)	1.13 ± 0.18*	76.68*	1.16*	5.62*	2.19*

<sup>a</sup>Values represent the mean ± SEM, for 5 animals per group. \* p<0.05 with control (student t-test followed by ANOVA).



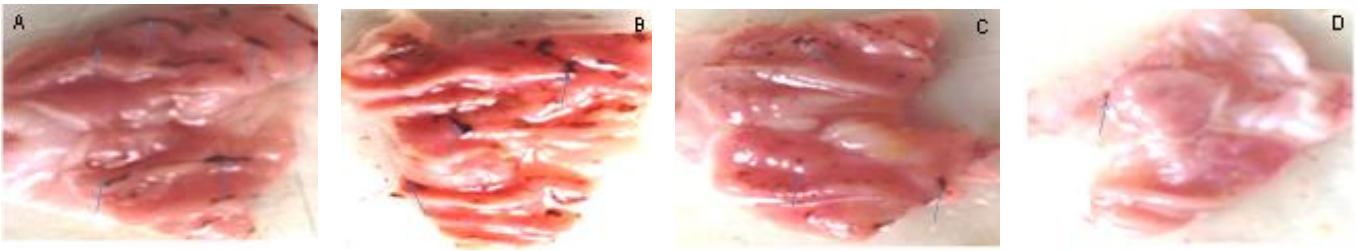
**Plate 1:**  
Effect of risperidone on WIRS-induced gastric ulceration



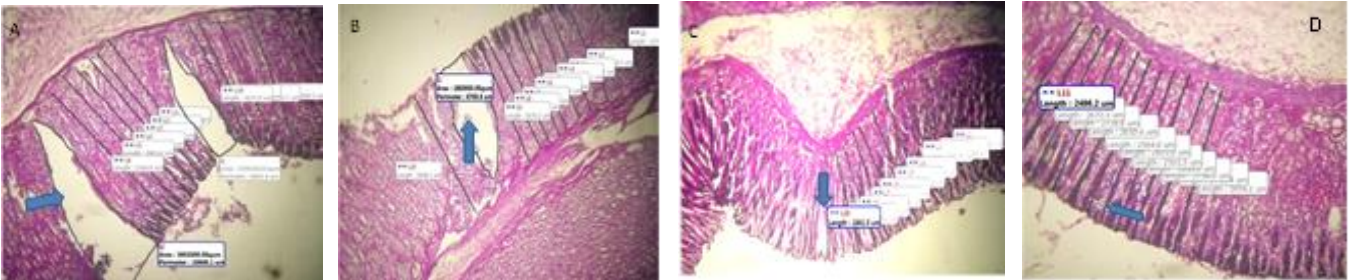
**Plate 2:**  
Histological profile of the effect of risperidone on WIRS-induced ulcer. H&E and PAS stain (x100).



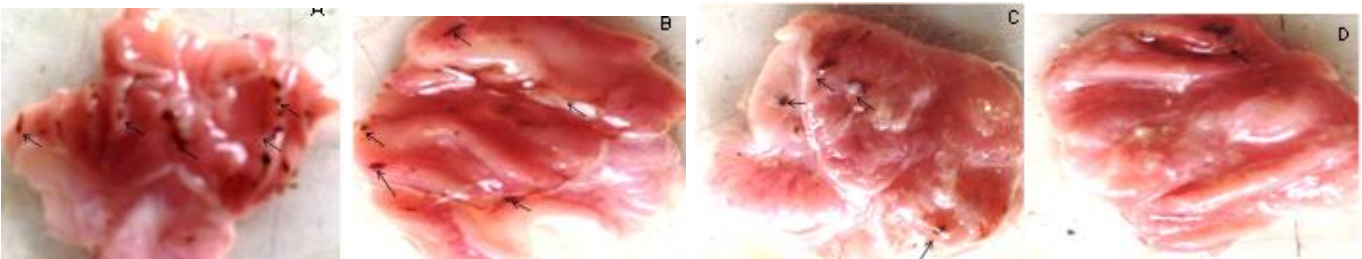
## Antiulcer properties of risperidone



**Plate 3:**  
Effect of risperidone on indomethacin-induced gastric ulceration



**Plate 4:**  
Histological profile of the effect of risperidone on indomethacin-induced gastric ulcer. PAS Stain (x100).



**Plate 5:**  
Effect of risperidone on starvation induced ulceration



**Plate 6:**  
Histological profile of the effect of risperidone on starvation-induced ulcer. H&E and PAS Stains (x100).

## DISCUSSION

The results of this study revealed that the three methods adopted to induce gastric ulcer affirmed that risperidone at all doses used showed anti-ulcer activity. It was observed that risperidone significantly reduced ulcer scores, ulcer area ( $\mu\text{m}^2$ ) and perimeter area ( $\mu\text{m}$ ) in a dose-dependent fashion compared to control in all

models. Earlier study had reported risperidone-treatment to alleviate stress-induced ulcers with increase in plasma levels of corticosterone, norepinephrine, glucose and total cholesterol using stress models (Saxena and Sanjay, 2011). These hormones are involved in stress. The degree of inhibition of ulceration increases with increase in the dose of risperidone given. This was explained from the work of Byun *et al.*, (2007), that corticosteroids

are involved in stress-induced gastric ulceration in rats. Stress has been reported to be one of the aggressive factors and it underlies many other diseases apart from ulcers and is one of the most commonly used methods to produce ulcer models (Kwiecień *et al.*, 2007; Brzozowski *et al.*, 2008). The ischemia that results from stress has been reported to generate free radicals leading to oxidative damage and thus ulcer formation (Olden, 2005). Other reports equally show that certain antipsychotics such as perospirone do have anti-ulcerative effects (Olden, 2005). From this study, risperidone ability to cause gastroprotection may be by either reducing plasma corticosterone level or reducing the generation of free radicals.

Risperidone significantly decreased the mean ulcer score, ulcer area ( $\mu\text{m}^2$ ), percentage ulcer area and perimeter ( $\mu\text{m}$ ) of ulcer in a dose-dependent manner in starvation-induced ulcer model compared to control. This model of ulcer induction are in agreement with other works (Elegbe, 1978) that reported that seven-days period of starvation consistently produced gastric ulceration in rats, and also that all the ulcers produced by this method occurred in the ruminal portion of the stomach of the rats (Robert and Nezamis 1958). They observed that the mechanism(s) whereby prolonged starvation causes gastric ulceration may be due to an impairment of the gastric mucosal resistance to the acid content of the gastric juice or to an enhanced corrosive (i.e ulcerogenic) effect of the normal gastric juice. Even though some studies (Robert and Nezamis 1958; Elegbe, 1978) reported the effect of the onset of ulceration beyond five (5) days of starvation, this work modified this ulcer model by examining the percentage ulcer area and perimeters of ulcer produced. This present study remarkably confirmed ulcer as from day six (6) and death on day seven (7). In the previous works, percentage ulcer area and perimeter of the ulcer were not calculated. In this study, the percentage ulcer area in resperidone pre-treatment were noticed to decrease 24% (0.1 mg/kg), 11% (0.3 mg/kg) and then to 5.6% (0.5 mg/kg), while the perimeter of the ulcer ( $\times 10^3 \mu\text{m}$ ) decreased from 8.43 in control to 3.44 (0.1mg/kg), 2.89 (0.3 mg/kg) and then to 2.19 (0.5 mg/kg). With this reduction in ulcer areas, risperidone is thus increasing or stabilizing gastric mucosal resistance to gastric corrosion. Furthermore, hypoglycaemia caused by starvation may result in copious secretion of gastric acid. The gastric acid back-diffusion and free radicals, these two offensive factors are related to ulcer formation may come into play (Davenport and Chavre, 1968). Since the integrity of the gastric mucosa is greatly affected by both offensive and defensive factors, it is conceivable that under normal circumstances, the pure gastric juice is

diluted and buffered by the swallowed food, water and saliva, mucus from the pyloric antrum and regurgitated duodenal secretions, thus reducing or neutralizing its corrosive effect on the gastric mucosa. With prolonged starvation, the above neutralizing factors are present in insufficient amounts, hence the gastric content approximates to the pure fundic secretion in its corrosive properties. Under this condition, the mucosa succumbs and an ulcer is formed. Since nutrients such as glucose and amino acids are essentials for maintaining homeostatic functions of gastric cells, it is possible that deprivation of food leads to pathological changes of the gastric mucosa. From the histopathological study there were reduced gastric ulceration in the entire risperidone pretreated groups compared to the control (Plates 1-6). Histological studies confirm these results by showing the occurrence of mucosal ulceration and the damage of epithelial and lamina propria cells in the control animals compared to the risperidone treated groups that showed a dose-dependent amelioration of ulcer. The various histological plates confirmed the strong role of risperidone at the micro level, that it can be effective in the complete prevention and healing of gastric ulcer.

From this study, risperidone in significantly caused a dose-dependent decrease in ulcer scores, ulcer area ( $\mu\text{m}^2$ ), percentage of ulcer area and perimeter ( $\mu\text{m}$ ) compared to the control in indomethacin-induced ulcer model and thus an increase in the ulcer protection. This is similar to a study by Cao *et al.* (2004) that reported pantoprazole sodium causing ulcer inhibition in aspirin-induced ulcer and that this effect is mainly due to acid inhibition. It is known that pure, undiluted gastric juice is an exceedingly corrosive fluid that can digest and destroy most living tissues, including the mucosa of the stomach. Risperidone may be mitigating some of these aggressive factors. Risperidone in reducing indomethacin-induced ulceration may be doing so by reducing MDA, a metabolite of TBARS, thus, further work in our laboratory will prove this.

This study provides evidences which suggest that risperidone which is used in the management of stress-related psychosis has anti-gastric ulcer effect in rats. However, more detailed studies are necessary to confirm the relevance of this finding and its implications in clinical settings.

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